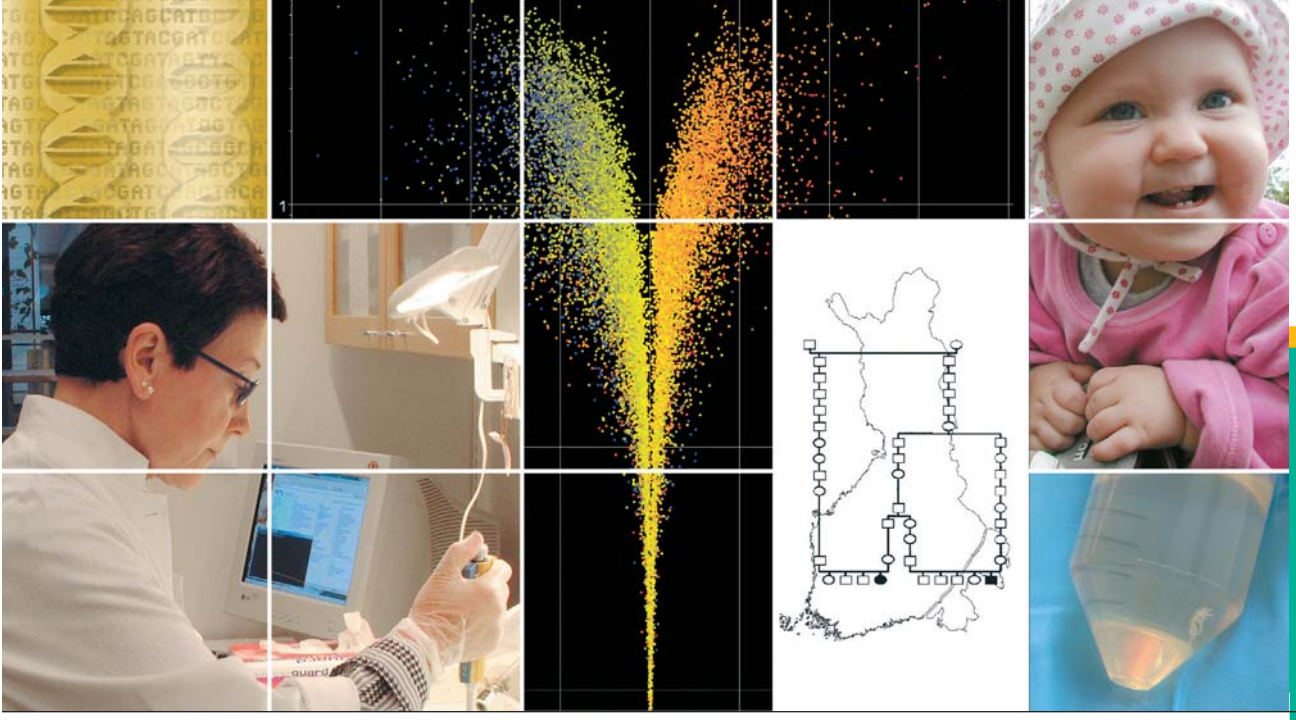

International Evaluation of the Department of Molecular Medicine National Public Health Institute

Kansanterveyslaitoksen Molekyylilääketieteen osaston kansainvälinen arviointi

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BACKGROUND MATERIAL FOR THE INTERNATIONAL EVALUATION

KANSAINVÄLISEN ARVIOINNIN TAUSTAMATERIAALI

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Background Material for the International Evaluation

Abstract

This review includes the material for the evaluation of the work of the National Public Health Institute (KTL, www.ktl.fi), the Department of Molecular Medicine (MLO, www.ktl.fi/portal/404) in 1997-2007. The main purpose of the evaluation is to guide the Ministry of Social Affairs and Health for the strategic management of KTL. A panel has been nominated to implement the evaluation. The panel members are Professor Albert Hofman (Erasmus MC, Rotterdam, The Netherlands), Professor Alan Wright (MRC, Edinburgh, UK), Professor Mart Saarma (University of Helsinki, Helsinki, Finland) and Chancellor Eero Vuorio (University of Turku, Turku, Finland). The evaluation panel will scrutinize the functions, strategic importance, scientific merits and the value for money of the scientific and expert work undertaken, and make proposals for future. In addition, a special attention is paid to the relevance and effectiveness of the work and of its impact on the health of Finnish people.

The goals of MLO are characterization of the molecular background of human diseases and producing of new data on the relationship between the genetic and life style risk factors that result in the health problems of Finns. Our internationally recognized research programs are focused towards the characterization of the molecular background of the Finnish disease heritage, cardiovascular diseases and neuropsychiatric diseases. Research data and expertise is provided for the national and international scientific community, for health care officials, for decision makers and for the general public. In addition, MLO produces novel knowledge of wide-scale genomic and biocomputational analyses for other investigators and research groups.

In 2006, MLO had personnel of 142 employees, out of which 43 with governmental funding and 99 with competitive external funding. The operating costs from the government budget has been 1.6–2.7 million Euros in 1997-2007. In 1997-2007 the competitive external funding has varied between 0.6–2.7 million Euros per year (25-56% of the total funding), being on an average 1.6 million Euros per year (44% of the total funding) during this same period. Within this decade MLO has produced 623 international peer reviewed articles, 65 international review articles and 17 articles in Finnish journals. In addition, 21 international and 10 domestic book chapters have been produced. Total of 61 Ph.D. theses have been compeleted during this period.

MLO has three research programs: 1) Genetic epidemiology, 2) Molecular biology of cardiovascular diseases and 3) Finnish disease heritage. The department also houses three core facilities or technology platforms that serve the wider research community: Bioinformatics core, Biotechnology core and Large Scale DNA Extraction and Storage Facility/National Biobank of Finland. Additionally, the Paternity Testing Laboratory has performed a legally determined function by offering the nationwide DNA-based paternity testing on a full cost-benefit basis.

Since June 1st 2007 the research programs and core facilities of MLO were strategically joined as a part of the Institute for Molecular Medicine Finland (FIMM). The Paternity Testing Laboratory was integrated into the Department of Research and Expertise Support Services (TASO).

Key words: molecular medicine, molecular genetics, Finnish disease heritage, coronary heart diseases, neuropsychiatric diseases, cellular biochemistry, bioinformatics, chip technologies, sequencing, paternity testing

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Molekyylilääketieteen osasto
Kansainvälisen arvioinnin taustamateriaali

Tiivistelmä

Tämä yhteenveto sisältää kansainvälistä arviointia varten kootun materiaalin Kansanterveyslaitoksen (KTL, www.ktl.fi) Molekyylilääketieteen osaston (MLO, www.ktl.fi/mlo) toiminnasta vuosina 1997-2007. Sosiaali- ja terveysministeriö odottaa saavansa arvioinnista tukea Kansanterveyslaitoksen strategiseen ohjaukseen. Arvioinnin tekevät professori Albert Hofman (Erasmus MC, Rotterdam, Alankomaat), professori Alan Wright (MRC, Edinburgh, Iso-Britannia), professori Mart Saarma (Helsingin yliopisto, Helsinki) ja kansleri Eero Vuorio (Turun yliopisto, Turku). Arviointipaneelin tehtävänä on tarkastella osaston toimintaa, strategista tärkeyttä, tieteellisiä saavutuksia, tieteellisen työn ja asiantuntijatyön kustannusvastaavuutta sekä tehdä ehdotuksia tulevaisuutta varten. Lisäksi kiinnitetään erityistä huomiota työn kohdentamiseen ja tehokkuuteen sekä sen vaikutukseen suomalaisten terveyteen.

MLO:n tavoitteena on selvittää kansantautien geneettistä taustaa ja tautien molekyylipatogeneesiä sekä tuottaa uutta tietoa, johon pohjaavat tulevaisuuden kansantautien diagnostiikka ja interventiostrategiat. Osaston tutkimus hyödyntää suomalaisväestön erityispiirteitä ja laitoksen keräämiä kansallisia erityisaineistoja. Osaston tieteellinen tutkimustoiminta liittyy KTL:n strategiassa määritetyille painoalueille, jollaisia ovat sydän- ja verisuonitaudit, metabolinen oireyhtymä, neuropsykiatriset sairaudet sekä suomalaisen tautiperimän sairaudet. Tutkimus- ja asiantuntijatietoa tuotetaan kansalliselle ja kansainväliselle tiedeyhteisölle, terveydenhuollon toimijoille ja päättäjille sekä suurelle yleisölle. Lisäksi MLO tarjoaa genomitietoon perustuvaa analytiikkaa sekä biolaskentaa muille tutkijoille ja tutkimusryhmille.

Vuonna 2006 MLO:lla työskenteli 142 henkilöä, joista 43 valtion budjettirahoituksella ja 99 kilpaillulla ulkopuolisella rahoituksella. Osaston vuosittainen budjettirahoitus on ollut 1.6–2.7 miljoonaa euroa vuosina 1997-2007. Vastaavana aikana vuosittainen kilpaillun ulkopuolisen rahoituksen määrä on vaihdellut 0.6 miljoonasta 2.7 miljoonaan euroon (25-56% kokonaisrahoituksesta) ollen keskimäärin 1.6 miljoonaa euroa vuodessa (44% kokonaisrahoituksesta). Kuluneen vuosikymmenen aikana MLO on tuottanut 623 kansainvälisen tieteellisen arviointikäytännön läpäissyttä artikkelia, 65 kansainvälistä katsausartikkelia sekä 17 kotimaista julkaisua. Lisäksi on tuotettu 21 ulkomaista ja 10 kotimaista kirjan kappaletta. Samana ajanjaksona MLO:ssa tehdyn työn tuloksena on valmistunut 61 väitöskirjaa.

MLO:lla toimii kolme tutkimusyksikköä, jotka ovat 1) Sydän- ja verisuonitautien molekyylibiologia, 2) Geneettinen epidemiologia, 3) Suomalainen tautiperintö sekä kolme tutkimuksen tukiyksikköä: Biologisten näytteiden logistiikkayksikkö/Kansallinen biopankki, Bioteknologiayksikkö ja Genomi-informaatioyksikkö (yhteinen Suomen Genomikeskuksen kanssa). Lisäksi Isyystutkimuslaboratorio on suorittanut palvelutoimintana lakisääteisiä DNA-tutkimukseen perustuvia isyystutkimuksia.

1.6.2007 alkaen MLO:n tutkimus- ja teknologiset osaamisyksiköt liittyivät osaksi Suomen molekyylilääketieteen instituuttia (FIMM) ja Isyystutkimuslaboratorio siirtyi Tutkimus- ja asian-tuntijatyön tukiosastoon (TASO).

Avainsanat: molekyylilääketiede, molekyyligenetiikka, suomalainen tautiperintö, sydän- ja verisuoni-taudit, neuropsykiatriset taudit, biokemia, solubiologia, bioinformatiikka, geenisiruanalyysit, sekvenointi, isyystutkimus

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Folkhälsoinstitutet
Avdelningen för molekylärmedicin
Bakgrundsmaterial för internationell utvärdering

Sammandrag

Detta sammandrag innehåller materialet som är samlat för den internationella utvärderingen av verksamheten på Folkhälsoinstitutets (KTL, www.ktl.fi) avdelning för molekylärmedicin (MLO, www.ktl.fi/portal/3480) under åren 1997-2007. Utvärderingens syfte är att fungera som en vägledare för Social- och hälsoministeriet och planeringen av den strategiska förvaltningen av KTL. Följande personer har utnämnts till panelmedlemmar: professor Albert Hofman (Erasmus MC, Rotterdam, Nederländerna), professor Alan Wright (MRC, Edinburgh, Storbritannien), professor Mart Saarma (Helsingfors universitet, Helsingfors, Finland) och kansler Eero Vuorio (Turun yliopisto, Åbo, Finland). Utvärderingspanelens uppgift är att granska avdelningens verksamhet, strategiska relevans, veteskapliga meriter och kostnadsmotsvarighet för vetenskapligt och specialistarbete, samt framställa förslag för framtiden. Speciell tonvikt läggs på arbetets inriktning och effektivitet samt dess påverkan på finländarnas hälsa.

MLO strävar efter att klarlägga folksjukdomars genetiska bakgrund, samt att producera ny information som diagnostiken och interventionsstrategierna för framtidens folksjukdomar baserar sig på. Avdelningens forskning utnyttjar den finländska befolkningens särdrag och de nationella specialmaterial institutet inhämtat. Avdelningens vetenskapliga forskningsverksamhet hör till de prioriterade områden som definieras i KTL:s strategi, såsom hjärt- och kärlsjukdomar, metaboliska syndrom, neuropsykiatriska sjukdomar samt finländska ärftliga sjukdomar. Forskningsmaterial och expertis produceras för att användas inom nationell och internationell forskning, inom hälsovården, samt av beslutsfattare och allmänheten. Dessutom erbjuder MLO genombaserad analytik och bioberäkning för andra forskare och forskningsgrupper.

År 2006 sysselsatte MLO 142 personer varav 43 med statens budjetfinansiering och 99 med utomstående finansiering. Avdelningens årliga budjetmedel har under åren 1997-2007 varierat mellan 1.6–2.7 miljoner euro, och den konkurenssatta utomstående finansieringens årliga belopp har varierat mellan 0.6-2.7 miljoner euro (25–56% av totalfinansieringen), vilket utgör i medeltal 1.6 miljoner euro per år (44% av totalfinansieringen). Under de senaste tio åren har MLO producerat 623 internationella artiklar med peer review, 65 internationella översiktsartiklar, samt 17 inhemska publikationer. Därtill har 21 utländska och 10 inhemska bokkapitel publicerats. Sammanlagt 61 doktorsavhandlingar har producerats under denna period.

MLO har tre forskningsenheter, 1) Enheten för hjärt- och kärlsjukdomarnas molekylärbiologi, 2) Enheten för genetisk epidemiologi och 3) Enheten för det finländska sjukdomsarvet, samt tre enheter som stöder forskningsarbetet: Logistikenheten för biologiska prov/Nationell biobank, Enheten för bioteknologi och Enheten för genominformation (gemensamt med Finlands Genomcenter). Dessutom Laboratoriet för faderskapsundersökningar har utfört faderskaps-undersökningar som en avgiftsbelagd service.

Från och med 1.6.2007 anslöts MLO:s forsknings- och teknologienheter till Institutet för molekylärmedicin i Finland och Laboratoriet för faderskapsundersökningar till Service-avdelningen för forsknings och specialistarbete.

Ämnesord: molekylärmedicin, molekylärgenetik, finländska sjukdomsarvet, hjärt- och kärl-sjukdomar, biokemi, neuropsykiatriska sjukdomar, bioinformatik, array teknologi, faderskapsunder-sökningar

PREAMBLE

In the early 1990s the Science and Technology Policy Council in Finland encouraged the Ministries to evaluate research institutions in their jurisdiction. In accordance to this policy, the Medical Research Council of the Academy of Finland carried out an evaluation of the research activities of KTL in 1994–1995, in response to a proposal put forward by the Finnish National Public Health Institute (KTL) and the Ministry of Social Affairs and Health (STM). The objective of this evaluation was to provide information on the public health functions, strategic importance, scientific merit and value for money of the scientific work undertaken and to make proposals for future work.

The international Evaluation Panel, chaired by Dr. David Evered of the UK Medical Research Council, prepared an evaluation Report to the Academy in October 1995. For the evaluation, KTL prepared a report describing the work in the Institute. The Evaluation Panel worked via internal meetings, discussions with important stakeholders of KTL, and through site visits to the three divisions of KTL. On the basis of their evaluation, the Panel made 35 major recommendations for further development of the organization, management and work of the Institute. Overall, the evaluation of the Department of Molecular Genetics and related operations of KTL were extremely favorable. The Panel made also some suggestions concerning the organization of the Departments and setting distinct priorities for the research so that they would be harmonized with the mission of KTL.

Over the past 10 years, most of the recommendations made by the Panel have been implemented: the organization of KTL has been changed, several areas of research and public health work have been directed towards new priorities, and more emphasis has been put on the public health impact of the work of KTL. In addition, a renewed strategy was prepared for the Institute in 2001 during a thorough process involving the whole organization. At the end of 2003, a new Director General was appointed to KTL.

Based on these developments, and on changes in the environment, time is ripe for a new evaluation of KTL. The purpose of such an evaluation would be to evaluate the effectiveness of the work and assess the scientific and societal impact of the Institute.

KTL IN BRIEF

Strategy and functions

The mission of KTL is to protect and promote the health of the Finnish people. As a research and expert institute belonging to the Ministry of Social Affairs and Health, KTL is responsible for providing decision-makers, professionals and citizens with the best possible health-related information for their choices. A general strategy for the Institute was prepared in 2001, while detailed objectives for the work are agreed upon annually with the Ministry.

The three main areas of work in KTL have traditionally been: 1) infectious diseases and immunizations, 2) chronic diseases and health promotion, and 3) environmental health. In all these areas, both research and public health functions are carried out. Activities of the Institute include basic research, ranging from the detailed analysis of the molecular

mechanisms of pathogenesis to large scale epidemiological and preventive studies and research into factors influencing health.

KTL monitors public health, diseases and their determinants through surveys and registers. Research and expert information is transferred into action by developing health-promoting and preventive measures and by advising and collaborating with various stakeholders. National vaccine service, many centralized laboratory functions and forensic medicine investigations are some of KTL's service functions.

Several of KTL's functions are based on laws, such as surveillance of infectious diseases and protection from communicable diseases by vaccinations. In the prevention of chronic diseases KTL works in close collaboration with various Non-Governmental Organizations. In promoting healthy environment and preventing diseases KTL collaborates with environmental authorities and municipalities. A strong presence in the media is a way to reach the people. The ultimate goal is to reduce the human suffering and economic cost caused by illness and to help people enhance their quality of life.

Organization, personnel and budget

KTL's main facilities are located in Helsinki and three other facilities in Kuopio, Oulu and Turku. The Institute has 11 departments, each of which is built of various laboratories and units. Ultimate responsibility of leading and managing the whole Institute rests on the Director General of KTL. He is assisted by the Deputy Director General, the Administrative Director and the Steering Group, consisting of the Directors of Departments. The Director General is also advised by a Scientific Council of KTL, where representatives of most important stakeholders are present.

At the end of 2006, KTL had a staff of 980 persons, of whom 450 were scientists or experts. Women make up 73% of the staff. In addition to the permanent or temporary staff, KTL is also a working place for non-paid students or scientists who pursue their studies and research together with the staff of KTL. Altogether, there were 158 Ph.D. students working at KTL in 2006.

The total expenditure of KTL was 66 million euros in 2006, and the operating expenses were 54 million euros when the acquisition of vaccines is excluded. Most part (62%) of the operational funding comes from the national budget, 29% from external sources like the Academy of Finland, the European Union, US National Institutes of Health, or various Foundations supporting scientific research. The rest 8% of KTL's budget is covered through income from chargeable services and from miscellaneous other funding.

EVALUATION PROCESS

Scope and purpose of evaluation

The objective of the review is to provide an evaluation of the work of KTL for the Ministry of Social Affairs and Health. The evaluation should examine the functions, strategic importance, scientific merits and value for money of the scientific and expert work undertaken, and to make proposals for future work. A special emphasis will be placed on the evaluation of the relevance and effectiveness of the work and of its impact on the health of Finnish people.

The evaluation and the Evaluation Report should address the following main issues:

a.	National relevance and effectiveness of the activities
b.	Appropriateness and adequacy of the research, expert functions and services
c.	Output and quality of research activities
d.	National and international co-operation
e.	Resource allocation
f.	Research fund raising
g.	Development needs, especially regarding processes and organization

The main purpose of the evaluation is to guide the Ministry of Social Affairs and Health so that they can use them for the strategic management of KTL. The practical implementation of the results, based on the decisions made at the Ministry, is the responsibility of the Director General of KTL.

Entities to be evaluated

The first round of detailed evaluations consists of four separate, partly parallel evaluations covering the main functional areas of KTL:

a. Environmental health
b. Chronic disease prevention and health promotion
c. Infectious diseases
d. Molecular medicine

After the first round has been completed, the entire Institute will be evaluated. This evaluation will focus merely on the general strategy, function and management of the Institute, with less emphasis on the evaluation of individual research and expert functions.

Information sources for the evaluation

KTL will provide the Panels following information:
Published documents concerning the whole Institute:

a. Annual Report 2006
b. Kansanterveyslaitoksen toimintakertomus ja tilinpäätöslaskelmat 2006 (available only in Finnish)
c. Evaluation of the National Public Health Institute of Finland. Report of the Evaluation Panel 1995

A document prepared by the Director of each relevant Department involved in the evaluation, will be provided for the evaluation. These documents describe 1) a report on progress in research over period 1997-2007 and research plans for the period 2007-2011, 2) the arrangement for governance and management, and 3) allocation of staff and resources, and 4) his/her plans for the future development of the Department.

Each Department involved in the evaluation will also provide the Panel a self evaluation of 1) the appropriateness of its work to the national public health needs, 2) its role in the dissemination of research results and knowledge and technology transfer, 3) a

description of the interfaces between the Department and the key players in Finland and abroad.

Evaluation of the Department of Molecular Medicine

The evaluation process was initiated in the Department of the Molecular Medicine (MLO) in 2006 after discussions in KTL's Steering Group and with the group leaders and core unit heads of the Department. The panel consists of two members, two from abroad and two from Finland. All the panelists are familiar to governmental health research, and the Finnish members will provide to the panel especially the knowledge of the national needs. Professor Albert Hofman from the University of Amsterdam, Netherlands, Professor Alan Wright from MRC center, Edinburgh, UK, Chancellor Eero Vuorio from the University of Turku, Finland and Professor Mart Saarma, Director from the Institute of Biotechnology, University of Helsinki, Finland were invited to conduct the evaluation.

The next step of the evaluation is based on the review of the documents provided by the Department. During the site visit in September 2007, the panel members will have an opportunity to interview group leaders, investigators and the staff of MLO and discuss with representatives of key stakeholders and collaborators in relevant Ministries and University of Helsinki. Based on the review of the obtained documents, discussions, and site visit, the Panel will prepare a Report to the Ministry of Social Affairs and Health and to the Director General of KTL.

1 DEPARTMENT OF MOLECULAR MEDICINE (MLO)

1.1. Background

The current department of Molecular Medicine is a result of a merge of two previous departments of KTL: Department of Human Molecular Genetics and Department of Biochemistry. This administrative reconstruction was based on the recommendation by the previous international evaluation and took place in 2001.

Department of Human Molecular Genetics (founded in 1988, Director Professor Leena Peltonen) exploited the unique opportunities of the genetic isolation of Finland to analyse the genetic background of human disease. The main goal of the department was to characterize the molecular background of the diseases of Finnish disease heritage and via this effort to develop tools and analytical strategies for the identification of genetic and life style risk profiles in common multifactorial diseases, representing public health problems. Additionally, the department developed specific DNA test panels of disease mutations based on research findings for population based studies. The department served both researchers within the KTL and investigators nationwide as knowledge centre for human genetics-related molecular biology techniques. The main mission of the Department of Human Molecular Genetics was research and it had no public health responsibilities beyond being in charge for the DNA-based national paternity testing. Concerning the Evaluation of the National Public Health Institute of Finland, the Report of the Evaluation Panel 1995 concluded that the department had exploited effectively the Finnish disease heritage and in the field of common diseases had produced studies of the highest standard, especially in MS and bipolar disease. Specifically, the good

collaborations with the FINRISK study and the Department of Mental Health were attributed. The research in human genetics was considered of major potential significance for public health. The panel recommended that (i) there should be further investment in this group in view of the potential public health importance of research in human genetics, (ii) the KTL should consider developing mechanisms through further investment an collaboration to extend the range of studies on the structure and function of gene products, including the use of transgenic animals and (iii) these studies should be developed further through the development of screening and other programmes – particularly through collaborations with other groups in KTL which have the necessary skills in epidemiology and behavioural sciences.

Department of Biochemistry (Director Professor Christian Ehnholm) concentrated on three major research topics: Lipoprotein metabolism, lipoprotein genetics and cell biology. The major focus was on lipoprotein metabolism and genetic factors influencing the risk of cardiovascular disease. The cell biology research was directed to the study of intracellular membrane traffic and microsomal triglyceride transfer. The department was specialized also in extensive biomarker analyses of lipid metabolism supporting research projects nationwide. Concerning the Report of the Evaluation panel 1995, the research on lipoprotein metabolism was considered of high quality and the lipoprotein genetics of good quality. The quality of the cell biology research was considered impressive. The panel recommended that (i) a strategic reappraisal of the role of the KTL in cardiovascular research should be undertaken covering particularly the departments Epidemiology and Health Promotion, Human Molecular Genetics, Nutrition and Biochemistry with possibly some reconfiguration of departmental boundaries to meet the needs of the strategy more effectively and enhance critical mass in the key areas (ii) the professional staff of the Department should be encouraged to develop their own high quality research programmes with an overall strategic framework; (iii) the cell biology group should be strengthened.

Department of Molecular Medicine (MLO) was founded in 2001 by merging the Departments of Human Molecular Genetics and Biochemistry. The MLO moved to the new biomedical research building: Biomedicum Helsinki, located on the Meilahti medical campus, next to the University Hospital. The research activities of the MLO have been since organized into the major programmes that were identified as most relevant areas from the public health and scientific point of view.

1.2. Objectives and organization

Goals

The Department of Molecular Medicine (MLO) is dedicated to use the unique Finnish study samples and population cohorts to characterize the molecular background of human diseases. This includes efforts to produce new data on the relationship between the genetic and life style risk factors that result in public health problems. The obtained genome-wide information is further utilized to develop intervention strategies and more biology-related classification for diseases, potentially valuable to develop diagnostics. Our research programs are especially focused in characterization of the molecular background of Finnish disease heritage, cardiovascular diseases and neuropsychiatric diseases. The Department provides expertise in a wide scale of genomic and

biocomputational analyses for the national and international scientific community, for national health care officials, for decision makers and for general public.

Means

To guarantee the top level of expertise in modern genetic and biological analyses, MLO has built an infrastructure that facilitates the collection of genome-wide information on the genetic background of diseases as well as functional information on the molecules that are critical in the disease process. Furthermore, we have established necessary database and computational resources for the expert analyses of the massive amount of collected biological information. Our scientific expertise, technology platforms and large nationwide sample collections facilitate a highly competitive environment for research and education in molecular medicine of the 21st century.

Organization

The directors of the department of Molecular Medicine have been Christian Ehnholm (2001-2002), Leena Peltonen (2002-2004) and Anu Jalanko (2004-). The department consists of three research programs, three research infrastructure core facilities and the Paternity Testing Laboratory (until 31.5.2007) which provides a legally determined nationwide service function.

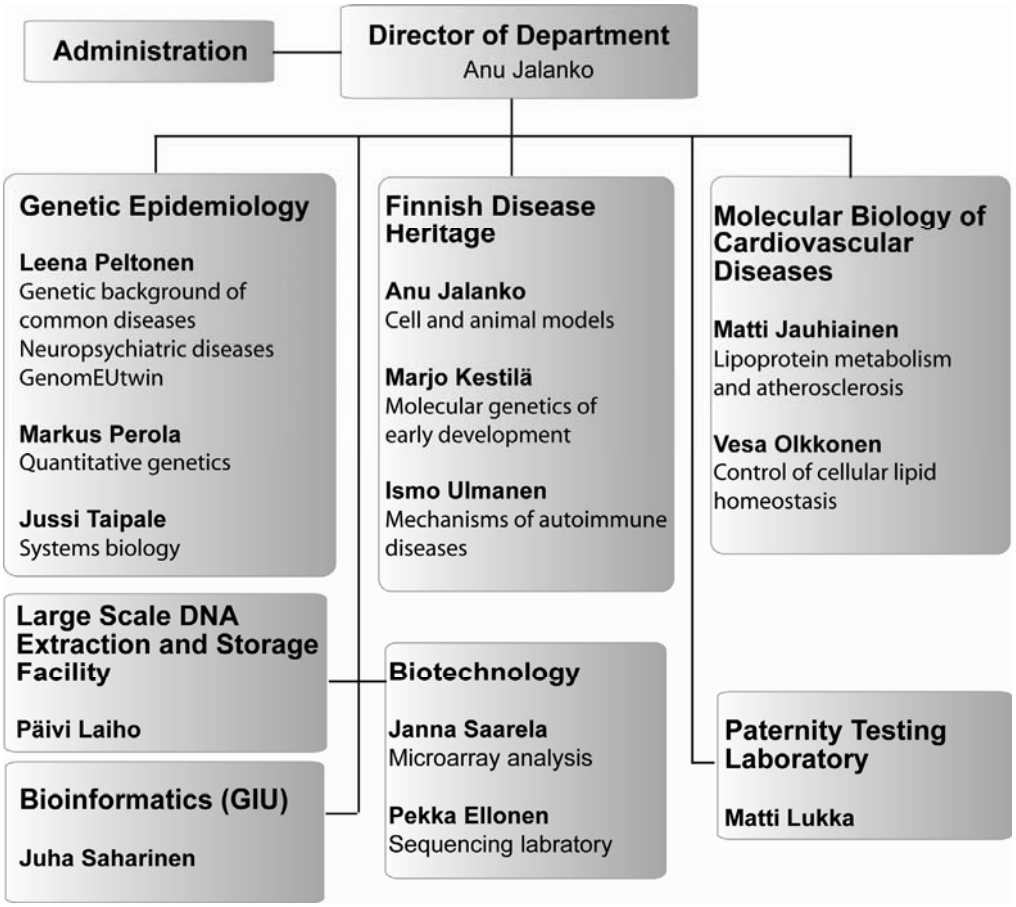

Figure 1. The organization of MLO in 2007.

1.3. Staff and resources

The staff of the department represents the personnel of the two departments: Human Molecular Genetics and Biochemistry during the years 1997-2000. In the year 2001 as the MLO was founded, the resources were combined to be exploited by the new department, with the exception of the Laboratory of Analytical Biochemistry that was allocated to the Department of Health Promotion. In the year 2005 the Research Unit of Immunology was transferred to the department of Virology and Immunological Diseases (VIMO) and is not included in this report.

The development of personnel of the MLO from 1997 to 2007 is presented in Table 1. The annual governmental budget has been varying between 1.6-2.7 million euros during the last ten years (Table 2.) and the external funding has increased from 0.6 million euros to a quite stable 2.6 million euros, e.g. 55% (year 2007) of the total funding including rents and equipments (Table 3.). Internal services (management help, animal facility support, media kitchen, library services) are not included in the sum.

Table 1. Development of personnel of the Department of Molecular Medicine* from 1997 to 2007.

	1997	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
Permanent											
Head of research group or laboratory	6	7	6	5	5	6	8	8	9	10	10
Senior researchers	2	2	2	3	3	3	3	2	0	0	0
Researchers	2	2	2	2	2	2	2	2	2	2	2
Administrative staff	2	2	3	3	3	3	2	2	4	5	6
IT personnel	0	0	0	0	1	1	1	1	1	2	2
Technical assistants	16	16	16	16	19	19	21	21	23	24	24
Together	**28**	**29**	**29**	**29**	**33**	**34**	**37**	**36**	**39**	**43**	**44**
External funded											
Head of research group or laboratory	1	1	2	1	2	2	2	2	2	2	3
Senior researchers	1	1	1	2	4	4	7	9	10	11	9
Postdoctoral researchers	4	4	11	10	4	4	6	4	3	6	7
Administrative staff	0	0	0	0	0	0	0	0	1	2	2
IT personnel	1	1	1	1	1	2	2	2	7	7	6
Students	28	29	25	25	25	25	47	55	64	65	61
Technical assistants	2	2	2	2	3	4	4	5	4	6	7
Together	**37**	**38**	**42**	**41**	**39**	**41**	**68**	**77**	**91**	**99**	**95**
TOTAL	**65**	**67**	**71**	**70**	**72**	**75**	**105**	**113**	**130**	**142**	**139**

* In 2001 two departments - Department of Biochemistry (BIOS) and the Department of Human Molecular Genetics (LMGO) - were merged and the Department of Molecular Medicine was established.

Table 2. Governmental budget (k€) of the Department of Molecular Medicine from 1997 to 2007 *(not corrected for inflation)*.

	1997	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
Salaries of permanent personnel	758	780	803	826	822	822	1083	1083	1083	1083	1083
Funding for running costs	385	385	385	385	385	385	385	385	385	385	385
Equipment and biobanking	759	781	803	374	202	200	200	786	874	809	200
Rent	-	-	-	-	384	384	384	384	384	384	384
TOTAL	**1902**	**1946**	**1991**	**1585**	**1793**	**1791**	**2052**	**2638**	**2726**	**2661**	**2052**

Table 3. External funding (k€) of the research programs from 1997 to 2007. The figures show the total amount of competitive external funding obtained in that year (one grant is typically for two to four years).

	1997	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
Finnish disease heritage	159	159	290	483	507	478	343	715	850	821	556
Genetic epidemiology	158	231	181	355	278	642	826	953	1424	1653	1600
Mol. biol. of cardio-vascular diseases	315	315	432	516	420	480	436	427	377	267	421
TOTAL	**632**	**705**	**903**	**1354**	**1205**	**1600**	**1605**	**2095**	**2651**	**2741**	**2577**

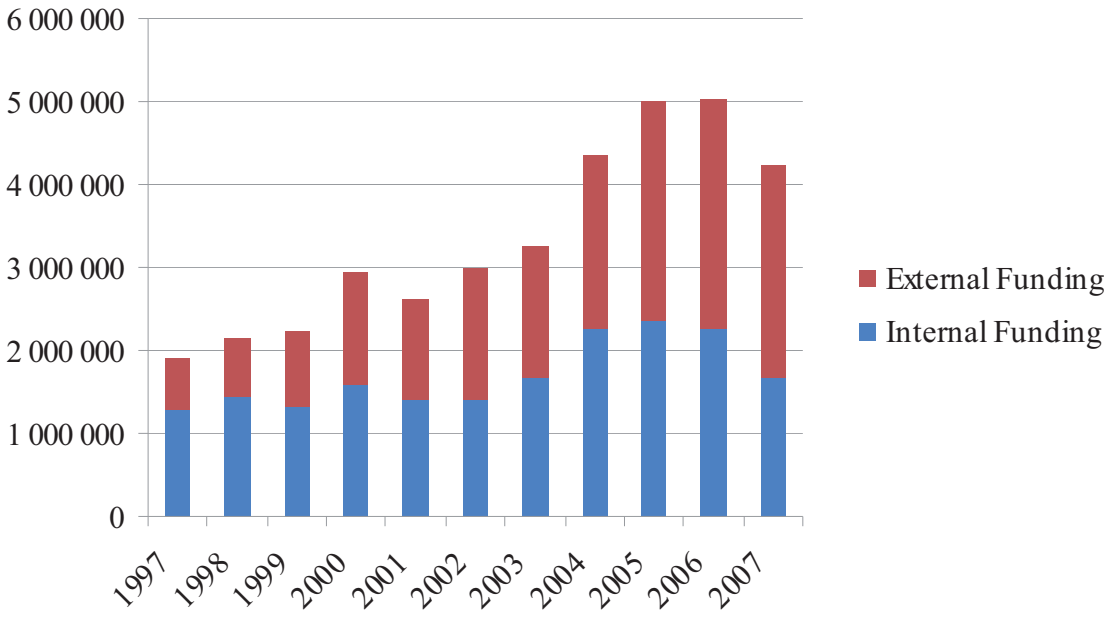

Figure 2. Total annual budget of the Department of Molecular Medicine* in 1997-2007. *1997-2001 Department of Biochemistry and Department of Human Molecular Genetics

1.4. Research areas

The research programs (www.ktl.fi/portal/405) of the MLO utilize our internationally unique study samples, the Finnish health care system and our accumulated expertise in genetics, biostatistics and molecular analyses to tackle the genetic background of diseases important for the public health. The research programs focus in cardiovascular diseases, neuropsychiatric diseases and the Finnish disease heritage. The research programs of MLO utilize methods of molecular genetics, genetic epidemiology, biochemical analyses of cellular and animal models, bioinformatics and systems biology to investigate molecular background of human health and disease.

Genetic epidemiology

The research of genetic epidemiology is based on our access to well defined Finnish study samples including large pedigrees of specific diseases and nationwide epidemiological cohorts. The major research projects involve molecular characterization of hyperlipidemias, metabolic syndrome, multiple sclerosis and severe psychiatric disorders. Utilization of genome-wide marker maps, transcript analyses combined with new tools of biocomputing and biostatistics has resulted in the initial identification of numerous genes and loci associated with common diseases. This success is based on the efficient use of special population structure of Finland and actually provided new paradigms of the use of founder populations in disease gene identification. This research area has also remarkably contributed to the development of new technology for the collection and analysis of massive genome-wide information.

Systems biology

The systems biology research area was initiated in MLO with the recruitment of Professor Jussi Taipale in 2005. The research of his group aims at understanding of disease mechanisms and development of high content screening methods facilitating the identification of new disease genes and characterization of functions of genes and their regulatory elements. Development of novel methodology has already resulted in internationally recognized success.

Molecular biology of cardiovascular diseases

The genetic findings in lipid metabolism constitute the basis for the functional analyses aimed at understanding the molecular mechanisms behind cardiovascular diseases. This research area utilizes biochemical, cellular and animal models to tackle the basic lipid metabolism. Life style and nutritional risk factors are tackled utilizing nationwide sample cohorts and functional analyses.

Finnish disease heritage

The Finnish disease heritage consists of over 30, typically recessive inherited diseases, enriched in this founder population. They have provided a proof of principle of the efficient use of the unique population structure and sample resources in identification and characterization of disease genes, development of DNA-based diagnostics and revealing of metabolic pathways important for human health in general. This research utilizes cell and animals models and genome-wide functional analyses to follow the disease process in cells and tissues.

Research infrastructure: Core facilities and technology platforms

The bioinformatics unit (www.giu.fi) utilizes and develops genome-wide computational analyses for the research purposes of molecular medicine.

The biotechnology core facility (www.ktl.fi/portal/9086) develops and provides easy access for investigators to genome-wide methods in transcript profiling and characterization of copy-number and functional variations.

The DNA sequencing facility (www.ktl.fi/portal/10917) is a part of the biotechnology core offering high quality sequencing and genotyping services for the research community.

Large Scale DNA Extraction and Storage Facility/National Biobank of Finland (www.ktl.fi/portal/3416 (in Finnish), www.nationalbiobanks.fi) serves the research groups of KTL and universities in DNA biobanking. It is equipped with state of the art sample tracking system, automated DNA extraction equipment, liquid handling robots, storage facilities and data management tools for sample logistics and optimal confidentiality and quality control.

Paternity testing laboratory

The paternity testing laboratory (www.ktl.fi/isyys (in Finnish)) is a national service laboratory providing legally determined paternity-testing based on DNA-analyses.

1.5. Strategic planning and management

The Director General of the KTL distributes the overall resources between departments after acceptance of the annual strategic plan of each department. The steering group of MLO (program leaders and core facility leaders) meets the Director General once a year to present the yearly achievements and strategic plans for the next year. The internal allocation of the resources takes place upon the acceptance of the strategic plan and the Director General does not interfere with the internal allocation of resources. In the beginning of each year the director of department makes a proposal for the allocation of the institutional funds to the steering group of the Department that provides the feedback and then the budget is finalized by the department director. The Paternity Testing Laboratory (ITL) works on a full-cost basis. Once a year, the steering group of MLO holds a strategic brainstorming session to discuss future developmental needs of the Department. All research programs have their own strategy days also at least once a year. The Paternity Testing Laboratory is an accredited laboratory and they have several management meetings during the year and face a yearly assessment by the Finnish Accreditation Service (FINAS).

The steering group of the Department meets once a week to discuss urgent matters and plans. The information from these meetings is further distributed to the personnel and staff by the program leaders. MLO has a weekly department meeting for the whole personnel, where the director of department shortly informs about timely important matters. Three times monthly the department meeting contains a presentation by a) Invited lecturer of public health or nationally/internationally important research areas, b) Postdoctoral researcher of the MLO, c) Junior researcher of the MLO and d) Once a month the department meeting is devoted to general business matters presented by the director of the department (including meetings with the KTL board) and the department is introduced with latest scientific accomplishments: new publications in press, new grants and other celebrations involving the researchers of the MLO. This monthly meeting ends with free discussion and questions of important matters. The meetings are held in English to guarantee the participation of the non-Finnish scientists and students.

Each research program has a weekly meeting on managerial subjects. In these meetings the research progress of each project is followed thoroughly. Research core facilities usually have their meetings once a month, assessing mostly managerial issues. Each core facility also has a supervision group of scientists and stake holders that meets at least once a year. Additionally, graduate students and postdoctoral researchers have regular strategic planning meetings with the supervisors and members of collaborating research groups.

Every employee has a discussion once a year with his/her supervisor where they discuss about personal achievements, future plans, needs for further education etc. This is a part of the KTL salary and support system. Additionally, salary agreement is discussed once a year between each employee and the immediate supervisor or unit head, within the limitations coming from the general rules of KTL and the budget available. To make the process transparent, the overall ranking of the different personnel groups are discussed in the Department board meeting. The flow of the strategic management is presented in Figure 3.

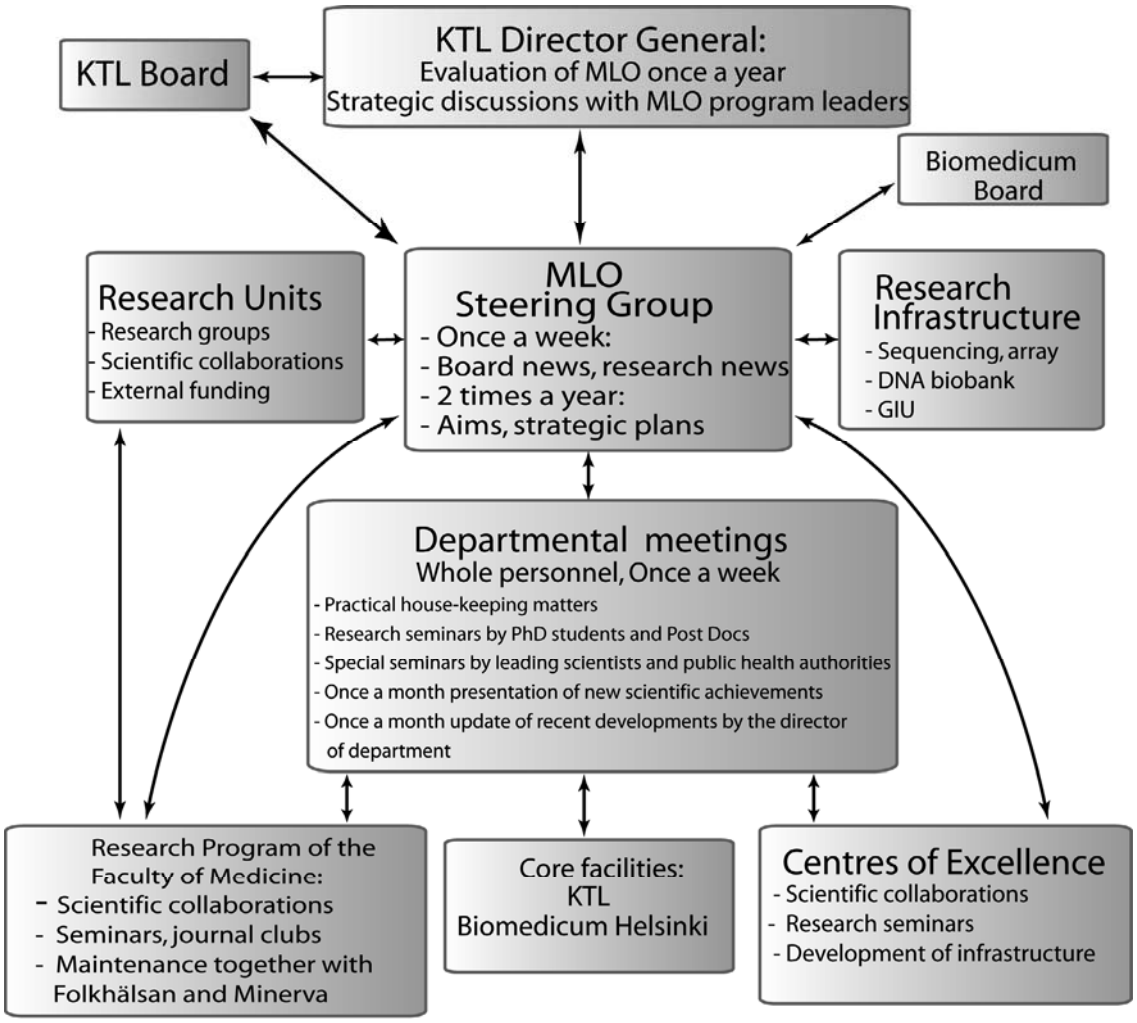

Figure 3. Strategic management of the MLO

1.6. Scientific impact of research

The MLO builds on the existing and integrated strengths of Finnish molecular genetics, epidemiology, biochemical expertise and biostatistics. The key investigators of the MLO include scientists with a worldwide recognized expertise and a strong track record in disease genetics, genetic epidemiology, systems biology, lipid biochemistry, cell biology, mouse models and biomathematics. Based on our expertise accumulated during research on the molecular basis of rare Finnish diseases, we have utilized the special Finnish population resources and established research programs in complex diseases affecting central nervous (CNS) and cardiovascular (CVS) system. These projects have produced new insights and understanding of the role of genetic profiles in human disease processes also more generally. The Department has a long tradition on tight national and international collaboration and the senior investigators are in the leading positions in many peer-reviewed prestigous research programs and networks including the Centre of Excellence in Complex Disease Genetics of the Academy of Finland, Nordic Centre of Excellence in Disease Genetics, Biomedicum Helsinki Research Programme on Molecular Medicine, Biocentrum Helsinki as well as in many EU projects and international networks.

The research programs of MLO capitalize on the possibilities provided by the special study samples collected by the MLO investigators and by KTL: The large pedigrees ascertained for familial types of common diseases, twin cohorts and epidemiological study samples collected from the Finnish population and representing a non-ascertained population sample facilitate both case cohort studies and longitudinal data analyses for quantitative traits. Detailed analyses of these study samples in an efficient way requires the most updated high-throughput genotyping, sequencing and transcript profiling methodology. The integrated expertise of the investigators at the participating umbrella organizations is critical for the application and further developments of high-throughput technologies. Finally, the integrated data analyses in these large study samples require construction and harmonization of databases and development of novel biocomputational and biostatistical strategies. Again, the pooled expertise of our national and international networks provide a solid basis for detailed genetic analyses of the large study samples and the necessary infrastructure for extensive genetic studies accessible to other investigators not only in Finland but also in other countries. The research tradition and research infrastructure of MLO has recruited numerous foreign students and scientists to Finland, most recently, the only Finnish Distinguished Professor of the Academy in Meilahti campus, Professor Joe Terwilliger. Research programs of MLO have also been the driving force behind the foundation of the Institute for Molecular Medicine Finland (FIMM). The FIMM, founded in September 2006 by the University of Helsinki (UH), the Hospital District of Helsinki and Uusimaa (HUS) and KTL is expected to further increase the visibility of genetic, epidemiological and translational research in Finland and strengthen recruitment of scientists around Europe.

Staff competence

We consider that the competence of the research staff in general has further improved during the last ten years. The number of citations of our publications has increased notably towards the end of the evaluation period. The increase is likely due to the fact that scientific requirements of KTL have been driven by a strong strategic vision of the institutional leadership. The best investigators in critical new fields are recruited and KTL has actively supported research careers and research training as an essential part of the departmental strategy. Importantly, we have focused on the increasing demands to train scientists in new skills of genome wide analyses, including high throughput screening, bioinformatics and systems biology. The total number of supervised Ph.D. theses was 61 during the past ten years, this would mean 8-10% of the Ph.D. theses of the Medical Faculty annually. The number of post doctoral researchers and senior scientists within the research groups has increased from 5 to 17 during the ten year period. Also, the number of junior investigators has increased remarkably since 2002 (Table 1.). The staff including technicians has also been offered systematic training programs in developing methodology and modern equipments involved in the analyses of modern genetics and biochemistry. Additionally, the competitive research environment in Biomedicum Helsinki has created pressure to develop the research careers for laboratory staff as well. The research infrastructure core unit concept, introduced by Professor Peltonen after her UCLA years (1998-2002) has generated novel working careers for bioanalytists and scientists as core facility leaders and laboratory project managers. The advancement of modern genetics has necessitated the recruitment of high level IT personnel, funded mainly from research grants and this has been a major contributor to our success in genetic epidemiology.

Investigators of MLO have succeeded very well in the highly competitive calls of research positions of the Academy of Finland. Two of the research group leaders are Academy professors (L.Peltonen (1.8.2003-31.7.2008) and J.Taipale (1.1.2008-31.12.2012)), the most prestigious academic position in Finland. In addition, during past 10 years two group leaders have been Academy Research Fellows, six investigators have been postdoctoral researchers and three group leaders have had a senior scientist grant of Academy.

Scientific productivity

The number of scientific articles in international peer review journals and domestic articles are shown in Table 4. If one article has authors from several research programs of the department, the article is counted to the most relevant unit based on subject. Thus, the sum numbers in Table 4. show the total numbers of articles published in MLO in each year.

Table 4. International peer review articles, reviews, book chapters and domestic articles and book chapters within different research units at the Department of Molecular Medicine published in years 1997-2007.

International peer review articles	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**Sum**
Finnish disease heritage	18	25	17	11	15	17	10	18	12	15	7	**165**
Genetic epidemiology	15	18	16	18	25	25	34	33	24	28	21	**257**
Mol. biol. of CV diseases	22	22	22	21	23	22	14	12	16	11	16	**201**
TOTAL	**55**	**65**	**55**	**50**	**63**	**64**	**58**	**63**	**52**	**54**	**44**	**623**

Review articles and book chapters	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**Sum**
Finnish disease heritage	3	4	3	1	4	2			2	2	2	**23**
Genetic epidemiology	4		1	3	2	2	1	2	2	4	6	**27**
Mol. biol. of CV diseases	4	2	3	7	3	3	3	5	1	3	2	**36**
TOTAL	**11**	**6**	**7**	**11**	**9**	**7**	**4**	**7**	**5**	**9**	**10**	**86**

Domestic articles and book chapters	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**Sum**
Finnish disease heritage	2						1	1			1	**5**
Genetic epidemiology		6		2	2	1	3	1		2	1	**18**
Mol. biol. of CV diseases	1			1		1			1			**4**
TOTAL	**3**	**6**	**0**	**3**	**2**	**2**	**4**	**2**	**1**	**2**	**2**	**27**

The mean impact factors of peer review articles per year are shown in Figure 4. The mean impact factor of all journals is 6.28 and 34 % of the all references present with impact factors over 7.

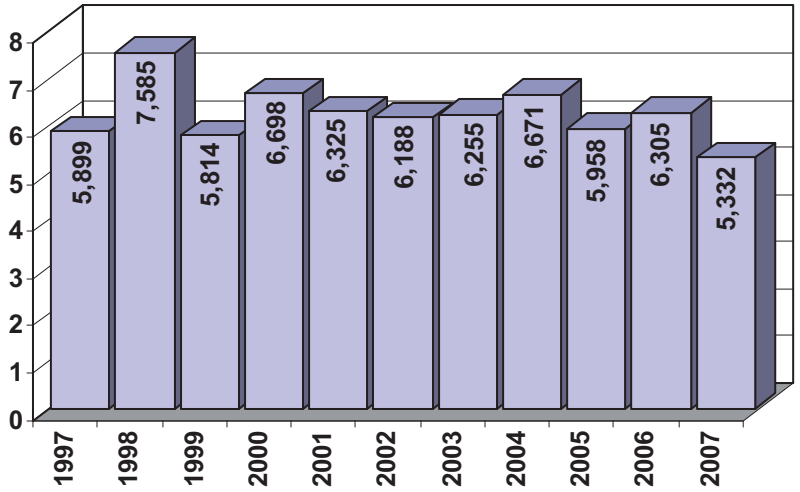

Figure 4. The mean impact factors in 1997-2007

Our researchers are actively supervising doctoral students working at the Department. Altogether 61 doctoral dissertations have been finished (the work done at MLO, see appendixes 1-3) during the last 10 years (Figure 5.). On average six Ph.D. dissertations have been completed annually.

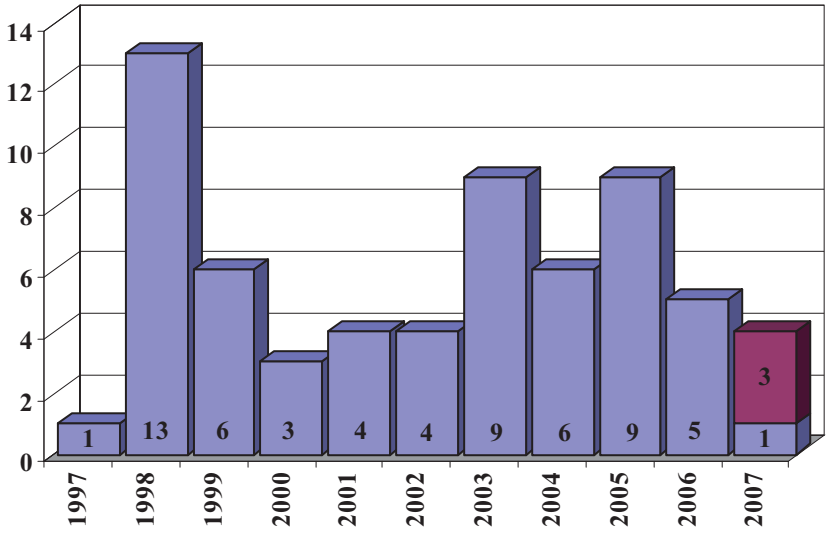

Figure 5. Number of doctoral dissertations at the Department of Molecular Medicine in 1997–2007. Upcoming dissertations are marked in purple.

1.7. Public health and expert functions

The main mission of the Department of Molecular Medicine is to perform top level research in the areas relevant for medicine and public health. Our goal is to collect new information and produce innovations that will guide public health decisions in future. The researchers of MLO participate in numerous national and international expert functions. At international level the most important current expert functions include the position of HUGO president held by Leena Peltonen, who also acts as the chair of the Strategic group of epidemiological research by Wellcome Trust. Leena Peltonen further acts as a board member of the European Research Council and as a chair of the governance body of the ESFRI Biobank initiative. She is also the only Finnish member of the Medical Institute of the National Academy of the USA. Research program leaders of the department have further held expert functions as evaluators in the 6th Framework Programme of the European Commission. At the national level, the researchers of the MLO have provided expert functions in the preparation of paternity and biobank law initiatives as well as given expert statements to the Board of Gene Technology.

The researchers of the MLO have further contributed to the production of the mission statement, strategy and founding documents of the Institute for Molecular Medicine Finland (FIMM). They have contributed to guidelines and quality control design strategies of biobank efforts nationally and internationally as well as to the development of ethical guidelines of the use of genetic information (e.g. Dr. Peltonen being a member of the UNESCO Bioethics Committee in years 1996-2002). In the local research committee the MLO investigators have contributed to the development of the Animal Centre of the University of Helsinki and strategic planning of the future fusion of the KTL animal facility to the Animal Centre of the UH. The main expert functions of the researchers of the MLO include pre-evaluations of several doctoral theses of different universities as well as acting as a dissertation opponent. As a major public health function, the researchers of the MLO regularly produce publications and give

oral presentations in meetings and congresses aimed to public health experts, researchers, patient organizations and general public. MLO investigators are frequently interviewed in radio and TV for their expert opinions in molecular medicine. The Finnish KTL Journal (www.ktl.fi/portal/12059 (in Finnish)) with a wide distribution among the Finnish biomedical community, has published articles presenting the EU projects of MLO as well as the research programmes of Finnish Disease Heritage, Genetic epidemiology, Systems biology and Molecular Biology of Cardiovascular Diseases.

1.8. Public health impact

The public health impact of the MLO is "future building", based on the enormous potential of modern human genetics and national sample cohorts to dissect the molecular background of common diseases. We recognize that there are major issues to be addressed prior to transferring new genetic or molecular discoveries to the health care system. These issues range from the essential step of validating the initial findings in multiple populations to the dissection of the genetic effect in relation to disease manifestations. Joint effects of genes, life style and environment, the cost implications of genetic testing and data delivery for the public in relation to benefits that could be obtained by the institution of traditional disease prevention measures, as well as the establishment of appropriate guidelines to inform health ministries, health care workers, patients and their relatives are also cited. Although it is acknowledged that several approaches are needed to discover and characterize every disease-susceptibility gene, there is a growing realization that the primary resource needed to address most of the above-mentioned issues are large collections of samples from human populations that include extensive clinical information (F. Collins, Nature, July 27, 2004). The common diseases studied by the MLO are major burdens to health care and society with prevalence figures for each selected target diseases being in the 2-10% range. Quantitative phenotype traits and mild subcomponents of the traits are even more common. MLO has identified and further aims at identifying susceptibility genes in all disorders under study by a combination of family- and population based genetic analysis in human study samples and to characterize some molecular mechanisms in detail using vast amount of genome tools available for mouse strains. Further, we are in the process to define the size of the genetic impact of identified allelic variants as well as to create some understanding of the tissue-and developmental stage character of the disease phenotype (e.g. characterization of specific triggers in molecular subtypes of disease).

The MLO utilizes the unique Finnish resources collected by highly professional Finnish clinicians and epidemiologists for the initial identification of genes and their specific alleles associated with specific complex diseases and their QTL component traits (often representing intermediate phenotypes). We further aim to obtain some understanding how alleles of various genes contribute to the genetic risk of these phenotypes. This novel information will be crucially important for future efforts toward more specific "molecular" diagnosis and improved treatment and care of these diseases. The data will produce accurate estimates for the prevalence, the distribution pattern and the effect of frequent gene variants (and combinations of gene variants) in the population contributing to biological diversity, health and disease (susceptibility and protection). It will also contribute to the understanding of the effect of frequent gene variants (and

combination of gene variants) on environmental exposure or life habits (such as diet, sedentary life style and smoking).

Inventions and innovations in this particular field are likely to result in new strategies in medical practice including new tools of diagnostics, treatment and intervention. The Nordic societies with their national health care system are in an excellent position to deliver the new possibilities of health care to individuals and the whole society. Thus the research carried out within the MLO will benefit not only the biotechnology and health care industry in Finland and other Nordic countries, but also European societies more broadly.

1.9. Participation in umbrella organizations and Centres of Excellence

Finnish Centres of Excellence (Academy of Finland)

Finnish centres of excellence are research units or researcher training units which comprise one or more high-level research teams that are at or near the international cutting edge of research in their field. These Centers are selected based on the international reviews of top experts in extremely competitive calls. In biomedicine there are total of 27 Centers of Excellence in Finland. The centre groups share a common set of objectives and work under the same leadership. Funding for centres of excellence comes not only from the Academy of Finland, but also from the host organisations of the units concerned. A centre of excellence may be a unit of research teams working at both universities and research institutes.

Center of Excellence in Disease Genetics (Academy of Finland, 2000-2005) was established to facilitate the maximal use of the potential of Finnish study resources and population structure in genetic research. The aim of this center was to utilize the specific features of the Finnish population: isolation, the small original population and the excellent health care system. In particular, the research carried out at the Center focused at understanding the function of the disease genomes damaging the central nervous system and at identifying the genetic component in diseases of Finnish disease heritage and common Finnish diseases with special competitive niche (families with multiple affecteds) such as multiple sclerosis, colon cancer and asthma. The Center was directed by Leena Peltonen (KTL) and other participating groups included: Lauri Aaltonen (UH), Anu Jalanko (KTL), Juha Kere (UH and Karolinska Institute) and Anna-Elina Lehesjoki (FH). Numerous disease genes were identified and the functional defects involved characterized by the investigators of this Center.

Center of Excellence in Complex Disease Genetics (Academy of Finland 2006-2011) (CoECDG, www.ktl.fi/diseasegenetics) aims to dissect genetic background of common diseases and their trait components by integrating special expertise and sample resources accessible to center investigators. The Center builds on accomplishments of the Center of Excellence in Disease Genetics of the Academy of Finland (years 2000-2005) but has a more extended research program to reflect the development of the field as well as its own research progress: from Mendelian diseases to complex traits. The major goal is to identify predisposing genes and their risk alleles for asthma, major cardiovascular and neuropsychiatric diseases. The center aims to capitalize the possibilities of the special population and epidemiological study sample resources of

Finland in genome-wide analyses using molecular methods, across species comparisons and biocomputational strategies.

The Center combines diverse expertise of eight group leaders across three academic institutes in Finland and one in Sweden: Leena Peltonen, (Director, UH and KTL), Jaakko Kaprio (Vice director, Department of Public Health, UH and KTL), Anu Jalanko (KTL), Juha Kere (Karolinska Institute and UH), Kimmo Kontula (Department of Medicine, UH), Anna-Elina Lehesjoki (FH and Neuroscience Center, UH), Aarno Palotie (Finnish Genome Center, UH), Joseph Terwilliger (Columbia University and Finnish Genome Center, UH).

Center of Excellence in Translational Genome-Scale Biology (Academy of Finland 2006-2011) (CoE in TGSB, www.tgsb.fi) has set itself the goal of studying the impacts of human genes on cell growth and premature ageing. The CoE in TGSB developes and applies high-throughput technologies to discover genes and signalling events that are responsible for cancer initiation, progression and for key cancer cell phenotypes. It translates the discoveries towards clinical and industrial applications. Finally, an important mission is the training of post-genome era young scientists. This CoE is a multidisciplinary effort that integrates biosciences, medicine, technology and informatics. It consists of six independently recognised research groups from the Universities of Helsinki and Turku and from the VTT Technical Research Centre of Finland.

The project is coordinated by Academy Professor Olli Kallioniemi (VTT Medical Biotechnology Centre, Turku). The other participating research groups include: Lauri Aaltonen (UH), Tomi Mäkelä (UH), Jussi Taipale (UH and KTL), Päivi Ojala (UH), Marko Kallio (University of Turku).

Nordic Center of Excellence in Disease Genetics (Nordiska ministerrådet 2005-2009)

The Nordic Centre of Excellence Programme in Molecular Medicine is a joint venture between the Joint Committee of the Nordic Medical Research Councils (NOS-M), the Nordic Council of Ministers and the Nordic Research Board (NordForsk). During 2005-2009, the Programme will support three new Nordic Centres of Excellence, NCoEs - networks of established Nordic researchers working together with common goals.

In the Nordic Center of Excellence in Disease Genetics (NCoEDG) (www.ncoedg.org) investigators from Denmark, Finland and Sweden, working in five Nordic Universities have pooled their expertise, methodological power and study sample resources to study the genetic background of metabolic syndrome, autoimmune and inflammatory diseases and colon cancer. The goal of the NCoEDG is to capitalize on unique resources of Nordic countries: Advanced molecular technologies, many developed by partners of NCoEDG, and advanced biocomputational analyses will be efficiently used to analyze large pedigrees of humans, ascertained for familial types of common diseases, the outbred stocks of farm animals and rodent strains produced for numerous complex diseases.

The detailed analyses of these study samples require updated high-throughput genotyping, sequencing and transcript profiling methodology. The collected expertise in clinical and molecular medicine and data analyses of the NCoEDG investigators is

critical for the next generation studies addressing the genetic etiology of common diseases. The most critical component for integration and analysis of these large study samples requires construction and harmonization of databases and development of novel biocomputational and biostatistical strategies. The pooled expertise of the NCoEDG and the complementary grant from Wallenberg Foundation to NCoEDG provides a solid basis for development of these critical infrastructure elements, not achievable by any group alone. The Nordic Center works like one integrated research group being linked virtually and via multiple annual workshops. Students and scientists visit other Nordic laboratories and the training program educates a generation of young scientists in new genome-wide approaches. The Center aims to create a unique scientific environment which could attract scientists and students also from outside Nordic countries. This would maximize our possibilities to solve the molecular background of these common diseases and use the inventions for the betterment of Nordic societies and health care. The NCoEDG comprises five Nordic centres with their repesctive leaders: University of Helsinki-Leena Peltonen (Coordinator), University of Uppsala-Ulf Landegren and Leif Andersson, Karolinska Institutet-Juha Kere, University of Lund/Malmö-Leif Groop and University of Århus-Torben Årntoft. A total of 21 research groups participate in this umbrella organization, three from the MLO: Peltonen, Jalanko and Taipale. The database structure of the Nordic Center has obtained substantial funding from the Wallenberg Foundation.

Biomedicum Helsinki Research Programme of Molecular Medicine (2001-2005 and 2006-2010)

The Faculty of Medicine has based on the competitive search and external evaluation selected total of six research programs to represent the flagships of it's research. Program of Molecular Medicine integrating basic genetic science discoveries with clinical medical research (and ultimate public health) is one of the original Programs in Biomedicum Helsinki. The first period of the program constituted years 2001-2005 and based on the evaluation of the international advisory board (headed by Erkki Ruoslahti) the programme was recommended to continue for the period of 2006-2011. The goal is to capitalize on the population-based, public health-based infrastructure in Finland to identify relationships between genomic composition of individuals and environmental/life style factors so as to define the molecular pathogenesis of common human diseases including the responses to intervention.

The Program of Molecular Medicine, led by Professor Leena Peltonen and Professor Kimmo Kontula interfaces and synergizes with the National Public Health Institute, Folkhälsan Institute, Finnish Genome Center, and Helsinki University Central Hospital. Core laboratories of international stature and utilizing state-of-the-art methodologies have been developed for (1) DNA-biobanking, (2) DNA sequencing, (3) microarrays, (4) bioinformatics.

The Program of Molecular Medicine is composed of ten interactive research groups, for the most part co-located within Biomedicum Helsinki:

Professor **Leif Groop**:Genetic complexity of type 2 diabetes and the metabolic syndrome
Dr. **Päivi Holopainen**: Molecular genetics of immunological diseases
Professor **Juha Kere**: Genetic research of complex diseases
Professor **Kimmo Kontula**: Molecular background of cardiac arrhythmias, essential hypertension, obesity and inflammatory bowel diseases

Professor **Anna-Elina Lehesjoki**: Mechanisms of neurologic disease: from gene mutation to molecular pathogenesis
Dr. **Hannes Lohi**: Canine models of human inherited diseases
Professor **Aarno Palotie**: Molecular genetics of migraines
Academy Professor **Leena Peltonen**: Genetic profiles of common diseases
Professor **Marja-Riitta Taskinen**: Cardiometabolical and genetical risk factors
Docent **Tiinamaija Tuomi**: Genetic complexity of diabetes

Biocentrum Helsinki

Biocentrum Helsinki is a large umbrella organization at the University of Helsinki, with some 530 people being engaged in research in biotechnology and molecular biology. The 26 member groups, selected based on the international evaluation, are located on two separate campuses of the University: Meilahti; Biomedicum Helsinki and Haartman Institute, and Viikki; Viikki Biocenter including Institute of Biotechnology and Neuroscience Center and Faculty of Agriculture and Forestry. The research activities at Biocentrum Helsinki range from human molecular genetics to plant biotechnology. Its purpose is to improve cooperation among the well-established research groups at the University of Helsinki, not only in conducting scientific research in the fields of biotechnology and molecular biology, but also in providing joint graduate training programs. The member groups in Biocentrum Helsinki have been selected by international experts strictly on the basis of their scientific accomplishments, providing that the work of the group is related to the fields of biotechnology and molecular biology. Professors Peltonen and Taipale from the MLO are members of this organization.

1.10. Research training and scientific meetings

Activity in teaching, training of graduate students and postdoctoral fellows

Each group of the Department has accumulated extensive experience in training of graduate students and postdoctoral fellows and the group leaders are all involved in one or several graduate schools. Professor Leena Peltonen has served as a member for the steering group of Helsinki Biomedical Graduate School (HBGS) in 1996-1998 and for the steering group of Helsinki Graduate school of Biotechnology and Molecular Biology (GSBM) since 2002. She established the graduate program in human genetics at UCLA in 1999 and was the member of the steering group of the campus-wide graduate program in genetics at UCLA in 1998-2002. Professor Peltonen serves on the Board of ComBi (Graduate School of Computational Biology) and GSBM (Helsinki Graduate School in Biotechnology and Molecular Biology). Drs Anu Jalanko, Matti Jauhiainen, Marjo Kestilä, Vesa Olkkonen, Markus Perola and Ismo Ulmanen have served as regular lecturers and experts in these graduate schools. Drs Aija Kyttälä (from Dr. Jalanko's group), Anu Loukola and Kaisa Silander (from Professor Peltonen's group) have been working as part-time coordinators in this Graduate School. The total number of supervised P.D. theses by the group leaders in 1997-2007 is 61. Our training is closely integrated with training provided by graduate schools. 30% of the graduate students of the MLO have been supported by one of the different graduate schools of the University of Helsinki. However, each graduate student of the Department has a possibility to apply to teaching events and courses arranged by graduate schools. Each student of the MLO has his/her thesis committee that meets annually to monitor the progress of the work. The Department maintains a continuous training program, involving weekly journal club sessions together with the Biomedicum Research

Programme of Molecular Medicine and Departmental research seminars. Additional method training sessions have been organized once month, featuring invited speakers from different core facilities and researchers mastering specific technologies.

Our international collaborations facilitate exchange both graduate and postgraduate students with other research institutes: Graduate training with UCLA became a tradition during Professor Peltonen's time there (total of 12 graduate students have experienced some time in UCLA and four UCLA graduate students have spent more than a year in MLO). Similarly, the exhange of postdoctoral fellows and junior scientists is taking place with the Broad Institute where Professor Peltonen holds a 18% visiting professorship. Total of six advanced graduate students or postdoctoral fellows have spents weeks or months at Broad and three postdoctoral fellows and junior scientists from Broad have spent various periods at MLO. Also via our EU supported integrated programs like GenomEUtwin and NCL-models as well as via the Nordic Center of Excellence special funds are targeted to the training of graduate and postgraduate students to guarantee the international links of our training program. MLO investigators have also organized two EMBO Practical courses in SNP genotyping and HapMap in 2005 and 2007. These international courses have been heavily oversubscribed and attracted a high number of students, postdoctoral fellows and junior scientists.

For postdoctoral students a more tailor-made training rotation to learn different methods within the Department is designed based on their expertise and research projects. The postdoctoral students are responsible for organizing and running the weekly journal clubs of complex diseases. They give their contribution to weekly seminars of the Department as well as in annual retreats in the form of scientific presentations describing their project. Each postdoctoral student will have in addition to his/her supervisor also a senior mentor from another group within the Department.

Scientific meetings and courses

The department has been a key contributor or the responsible organizer to 34 scientific meetings and workshops and seven training courses:

Scientific Meetings and Workshops:

- 5th International Symposium on the Marfan Syndrome, August 7-10, 1998, Helsinki, Finland
- The 69th European Atherosclerosis Society Meeting, May 24-26, 1998, Helsinki, Finland
- Scandinavian Society for Electron Microscopy, 50th annual meeting, June 7-10, 1998, Espoo-Helsinki, Finland
- Satellite symposium of the XIIth International Symposium on Atherosclerosis: High density lipoproteins and atherosclerosis, June 30-July 3, 2000, Helsinki, Finland
- The Annual Scandinavian Society for Atherosclerosis Research (SSAR) Meeting, May 30-June 2, 2002, Humlebaek, Denmark
- GenomEUtwin Phenotype Workshop: harmonization and better definition of the phenotypes. Statistical Genetics Short Course: state-of-the-art statistical genetics methods for detection of susceptibility loci for complex traits March 24-25, 2003, Helsinki, Finland
- HGM2003 – Human Genome Meeting, April 27-30, 2003, Cancun, Mexico

- The Annual Scandinavian Society for Atherosclerosis Research (SSAR) Meeting, May 22-25, 2003, Humlebaek, Denmark
- DNA 50 years Biomedicum Symposium, August 25, 2003, Helsinki
- HGM2004 – Human Genome Meeting, April 4-7 2004, Berlin, Germany
- 1st Millennium Technology Prize Symposium, June 13-16, 2004, Espoo, Finland
- GenomEUtwin: 1st Workshop on Logical Reasoning in Human Genetics, September 19-23, 2004, Helsinki, Finland
- GenomEUtwin Junior Investigators Workshop, December 13-14, 2004, Rome, Italy
- Public Population Project in Genomics (P3G), June 1-4, 2004, Helsinki and Tallin Workshop
- 11th International Symposium on Neuronal Ceroid Lipofuscinoses, June 5-8, 2005, Helsinki
- World Congress on Psychiatric Genetics XIII, October 14-18, 2005, Boston, USA
- NCoEDG - database expert meeting and student training, March 30 - 31, 2006, Lund, Sweden
- HGM2006 – Human Genome Meeting, May 31– June 3, 2006, Helsinki, Finland
- The English Speaking Working Group of International Society for Forensic Genetics, June 8-11, 2006, Tuusula, Finland
- 5th European Research Council Meeting, July 3-4, 2006, Helsinki, Finland
- GenomEUtwin 2nd Workshop Logical reasoning in genetics and genetic epidemiology, August 14-18, 2006, Helsinki, Finland
- NCoEDG database and bioinformatics experts meeting, August 24, 2006, Stockholm, Sweden
- Round table workshop on clinical experts and Intranet training of site experts, August28, 2006, Uppsala, Sweden
- 1st Nordic Meeting on Genetic and Pathogenesis Immunological Diseases, September 4-5, 2006, Helsinki, Finland
- World Congress on Psychiatric Genetics XIV, October 28 – November 1, 2006, Cagliari, Italy
- Nordic Centre of Excellence in Disease Genetics (NCoEDG), Junior scientist meeting, November 16-17, 2006, Malmö, Sweden
- XV Paavo Nurmi Symposium, December 13-15, 2006, Oulu, Finland
- GenomEUtwin Scientific Meeting, European network of twin registers and MORGAM cohorts, December 14-15, 2006, Rome, Italy
- NCoEDG database and Informatics meeting: Towards a Nordic Federated Network in Disease Genetics, March 6, 2007, Uppsala, Sweden
- European Research Infrastructure - Bio-Banking and Biomolecular Resources, Partner and Stakeholder Meeting, Vienna, March 17, 2007, Vienna, Austria

- HGM2007 – Human Genome Meeting, May 21-24, 2007, Montreal, Canada
- 3rd International Meeting on Genetics of Complex Diseases and Isolated Populations, May 26 – 29, 2007, Turin, Italy
- High Density Lipoproteins and Atherosclerosis, Satellite Symposium of the EAS Congress, June 7-9, 2007, Helsinki, Finland
- EAS 76th Annual Congress, June 10-13, 2007, Helsinki, Finland

Training courses:

- EMBO Practical course on SNP genotyping and haplotype analysis, August 21-27, 2005, Helsinki, Finland
- Advanced Techniques in Molecular Medicine, co-sponsored by EMBO, June 15-22, 2005, Uppsala, Sweden
- Applied bioinformatics and methodologies for SNP genotyping, November 12-18, 2005, Uppsala, Sweden
- Statistical Genetics Course, July 23-28, 2006, Stockholm, Sweden
- Logical Reasoning in Human Genetics and Epidemiology, August 14-18, 2006, Helsinki, Finland
- Applied bioinformatics and methodologies in SNP genotyping, March 10-15, 2007, Uppsala, Finland
- Course on RNA interference, June 6-12, 2007, Heidelberg, Germany

Upcoming meetings and training courses

- EMBO Practical Course on Genome-wide SNP Association Studies, August 27-31, 2007, Helsinki, Finland
- European Life Scientist Organization (ELSO) Meeting (Systems Biology co-organizer/chair, speaker), September 1-4, 2007, Dresden, Germany
- International Research Policy Conference – Excellence Stems from people, August 27-28, Turku, Finland
- Marie Curie workshop: Array techniques to identify copy number variations, September 10-15, 2007, Helsinki, Finland
- The 48th International Conference on the Bioscience of Lipids, September 4-8, 2007, Turku, Finland
- XVI International Symposium on Drugs Affecting Lipid Metabolism, October 4-7, 2007, New York, USA
- The International Atherosclerosis Society (IAS) Workshop on HDL, October 9-12, 2007, Santorini, Greece

1.11. Future directions and participation in the Finnish Institute of Molecular Medicine (FIMM)

Strategic joining of expertise and resources is the critical key to success for a small country. Within FIMM, MLO will serve even more efficiently the Ministry of Social Affairs and Health (STM), the international scientific community, national health care officials and the general public in the area of molecular medicine. We will continue to perform high quality research that gives us the expertise and credibility to advise both the ministry and the public. Especially we will serve the goals of the Biotechnology Strategy of KTL and the recently developed programs of the decision makers, aiming at producing scientific excellence by a novel strategic alliance between ministries.

We will challenge ourselves to maintain the international scientific excellence and the unique Finnish expertise in the analysis of environmental and genetic risk factors behind common diseases. The research will be based on the large national biobanks, representing a total of 200 000 samples representing population cohorts with detailed information of risk factors and traits of cardiovascular and neuropsychiatric diseases (www.nationalbiobanks.fi). The basis of the department will continue to be the

exploitation of new genome information and the built expertise in genetics, databases, biocomputing and functional analyses of disease mechanisms.

The most important strategic decision affecting the future of MLO is the strategic alliance between KTL and FIMM. KTL acts as a founding partner of FIMM together with University of Helsinki and the Helsinki and Uusimaa Hospital District. Regulations of FIMM were approved by the Senate of the University of Helsinki in December 2006. The collaboration agreement between KTL and FIMM will be signed by the rector of the university and the director general of KTL in August 2007. With this agreement the MLO will be strategically joined to the FIMM while the permanent staff of MLO will retain their employment in KTL.

FIMM aims at producing new information concerning the molecular mechanisms of disease development, taking advantage of clinical and epidemiological materials to detect, treat and prevent diseases and promote public health. An important mission of FIMM is to engage high-quality international research in clinical and molecular medicine, genetic epidemiology and to co-operate with national and international research centres. The FIMM aims at enhancing the research in the field and to develop infrastructure with universities, university hospitals, research departments and industry to create an internationally visible, multidisciplinary environment of excellence in science and technology. Furthermore, FIMM aims to promote research training and exploitation of research findings. The important added value of the FIMM is based on the strategic alliance between the university, state research centre and industry. It aims to network with centers of molecular medicine in Norway and Sweden and the final goal is to establish a Nordic node of EMBL in molecular medicine.

The strategic value of MLO within the FIMM will be based on the scientific excellence in genetic epidemiology and utilization of the KTL biobank materials and study samples. The success of the alliance will depend on efficient utilization of the biobanks in genetic epidemiology. Additionally, the existing expertise of MLO in biocomputing and database construction will be utilized and further developed. The efficient development of the genomic research involving biobanks in Finland is tightly encoupled with the success of the recently funded new European biobank initiative (ESFRI Biobanks Initiative, BBMRI). The Ministry of Social Affairs and Health is acting as the Finnish state representative of this initiative.

1.12. Facilities

The MLO is housed in Biomedicum Helsinki (www.biomedicum.helsinki) (located next the to the Helsinki University Central Hospital), a five story 24 000 net m^2 research building houses about 1200 research employees and over 200 research groups from several organizations (University of Helsinki (UH), National Public Health Institute (KTL), Folkhälsan (FH), Helsinki University Hospital). The Biomedicum Helsinki houses three centers of excellence of the Academy of Finland and investigators of Biomedicum direct of co-ordinate several EU projects and one Nordic Center of Excellence. This exceptional and interactive research environment is equipped with state of the art instrumentation which is

shared by groups. The department space of MLO contains 1322 net m^2. To facilitate modern, cutting edge biomedical research, Biomedicum Helsinki has invested to core facilities with newest technology and professional expertise in the use and further development of these technologies. These include:

1. **Clinical data collection facilities:** Immediate vicinity to the University Hospital and equipped appointment rooms for research subject visits in the proximity of research laboratories
2. **A large scale DNA extraction and storage facility of KTL/MLO/National Biobank of Finland** presently houses DNA from more than 200 000 individuals (www.nationalbiobanks.fi). It is equipped with state of the art liquid handling robots, storage facilities, an automated Gentra DNA extraction equipment and tailor made data management tools for optimal confidentiality and quality control and has a highly qualified, permanent staff of five technicians and a supervisor. The database management is harmonized between the DNA sample core, sequencing and genotyping units. It provides services on a subsidized recharge basis.
3. **The Finnish Genome Center** (FGC, www.genome.helsinki.fi) is an intellectual core facility to promote genetic research in Finland by providing genotyping services for both genome-wide scans and fine-mapping analyses. Multi-allelic genotyping is performed using automated liquid handling equipment and the ABI3730 Capillary Sequencer. Locus-specific SNP genotyping of tens of markers is performed using a Sequenom iPLEX assays. Larger locus-specific or genome-wide SNP studies are primarily performed using the Illumina Golden Gate Assays. Genome-wide SNP genotyping can also be performed using Affymetrix platforms. The work flow and day to day quality control procedures are performed using a LIMS system and genotype storage and subsequent handling for statistical analysis is performed by a unique, tailor made data base system which is generated by the Genome Informatics Unit.
4. **The Genome Informatics Unit** (GIU, www.giu.fi), a joint facility between the KTL/MLO and University of Helsinki, provides biocomputing expertise as well as computing resources for researchers in Biomedicum Helsinki and their collaborators to perform bioinformatics analysis in the areas of sequence analysis, gene expression analysis, genomic annotations as well as genetic linkage and association analysis. GIU provides its users the largest collection in Finland of the publicly available bioinformatics applications and databases in its focus areas and updates these frequently. These applications are generally available for MS Windows platforms as well as the traditional statistical data analysis packages, which are typically made for Linux/UNIX server environments. Since GIU has both the Linux and MS Windows Advanced server architectures, its users can employ the widest range of bioinformatics applications, made available over the Internet, using secure, graphical user interfaces.
5. **The Biomedicum Biochip Center** (BBC, www.helsinki.fi/biochipcenter) provides microarray core facility services for both custom made and Affymetrix arrays. It serves annually 60 research projects and performs over 2000 hybridizations. It operates on either full service or walk in and training modes. The BBC involves 10 scientists and technicians of whom two are full time for BBC. The core performs both service and research projects and provides hands on training in array technologies.
6. **The Sequencing Core** (www.ktl.fi/portal/10917), a joint facility between KTL/MLO, HUS, FH and Biomedicum Research Programme on Molecular Medicine, provides low cost, high quality sequencing services for Biomedicum researchers using an ABI3730xl 96-capillary instrument. In addition, small to medium scale fragment analysis service is available.

7. The Protein Chemistry Core of Biomedicum provides modern microchemical protein analyses as well as small to medium scale protein purification and isolation (research.med.helsinki.fi/corefacilities/pcf/). Special services include identification and sequencing of proteins, characterization of protein interactions and proteomics-based analyses of the samples. The unit also provides training courses in modern protein purification.

8. The Protein Interaction Facility of Biomedicum provides the yeast two-hybrid screening techniques to identify and clone interactive partners for proteins of interest (www.ltdk.helsinki.fi/res/makela/core/th.htm). The bacterial two-hybrid screenings are also being set up. The services include screening of appropriate cDNA libraries and the maintenance of several requisite cDNA libraries and cloning vectors.

9. Transgenic Mouse Facility and Vivarium: The animal facility in Biomedicum can host up to 4000 mouse and 300 rat cages, has a barrier, a conventional area, and a room for experiments with replication deficient viral vectors. A second, new vivarium available is located across the street in the Haartman Institute and includes a P3 facility. The Biomedicum animal facility has long experience in production of transgenic animals. The animal facility at KTL has an SPF barrier, several rooms for experimentation and follow-up of the mouse strains, a separate BL3 area for experiments with viral vectors and an injection facility. The KTL animal facility has successfully produced both transgenic and knock-out animals. The KTL animal house has a long tradition for inbreeding of different mouse strains. The animals from KTL are allowed to Biomedicum for example, for MRI analyses. Additionally, the KTL animal house contains a separate department for production of rabbit antibodies. A current effort between KTL and UH aims at joining the KTL animal facility to the newly established University of Helsinki Animal Facility, including also the Biomedicum vivarium. This should promote integration and cost effectiveness of the animal facility.

10. Functional MRI Unit of Biomedicum (www.miu.helsinki.fi): The 4.7 tesla fMRI equipment of this unit permits fast and accurate imaging of rodent organ structure and organ functions. The unit is a collaborative unit of the University Hospital and University.

The Epidemiological units of the UH and of the KTL, including the Finnish Twin Cohort and their host departments are located just north of the Biomedicum facility, but joined by high-speed computer links and easily accessible by a short walk or car ride. The facilities contain up to date computing equipment, and support staff include both computer scientists and biostatisticians. There is also room for expansion, and current plans at the National Public Health Institute are to build in the very near future a new building to house both of these epidemiological units. The twin study has also extensively collaborated with other investigators to permit appropriate phenotyping of traits; in recent years imaging techniques (MRI, FMRI, PET etc), and clinical investigations have been integral parts of substudies of the most informative twin pairs and families. For these, subjects have attended facilities at different parts of the medical campus or elsewhere at the University.

2 BIOTECHNOLOGY

2.1. Research area and its significance

The Human Genome Project and the HapMap project have produced a high number of catalogued sequence variants enabling genome-wide studies of genetic loci behind common disease-related phenotypes. However, identification of genetic factors predisposing to these multifactorial diseases, like diabetes, cardiovascular disease, metabolic syndrome, neurological diseases and mental health problems, requires usage of genome-wide analysis methods in large sets of samples. Rapid development of genome wide analysis techniques during the last 10 years and requirement for substantial financial investment related to the high though-put technologies favors centralization of both the instruments and the special know-how to core facilities.

The aim of the Biotechnology core facility is to develop and to provide easy access for investigators to genome wide methods in transcript profiling, sequencing and characterization of copy-number and functional variations. As mere service units seldom can operate in the international frontline of the technology development, the Biotechnology core is highly integrated into the scientific projects. This facility brings genome wide expertise to research projects nationwide and trains/educates researchers in utilizing genome wide methods: sequencing, genotyping and gene expression analysis on microarrays and other medium to high through-put platforms. The chip-based operations of the Biotechnology core facility contribute to the functions of the Biomedicum Biochip Center core unit. Tight integrations and database harmonization with the Finnish Genome Center guarantee the seamless operations of these genome analysis units of Biomedicum.

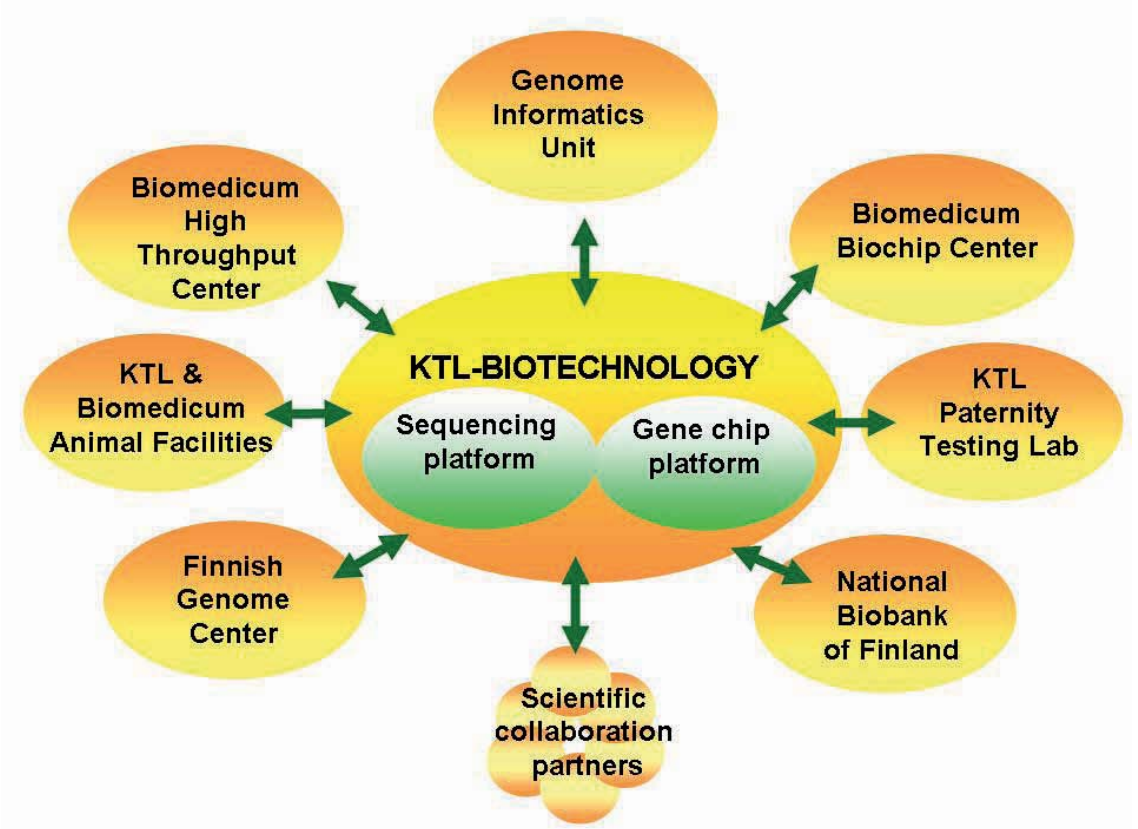

Figure 1. Interactions of the biotechnology core operations

Emerging new technologies need to be evaluated and certain supportive technologies and automation has to be developed/set up before even the commercially available methods can be adapted in large studies. The Biotechnology core develops and evaluates supportive techniques and provides expertise in setting up the automation for different platforms. Furthermore, genome-wide analysis methods create large amounts of data, thus the core works in close collaboration with the Bioinformatics core to develop software and database solutions for data storing and analysis. Rapidly increasing information of the structural or functional variability within the genome will greatly affect the interpretation of data.

2.2. The main achievements

Biotechnology core operations of MLO were initially established in the first quarter of 2001 when the department moved to Biomedicum. The core facilities represent a natural extension to continuous method development process that has been a strong part of the department of Human Molecular Genetics since its foundation 1988. First task of the core during 2001-2002 was to set up a microarray facility for the Biomedicum research community. An Omnigrid microarrayer (GeneMachines) was acquired 2001 to enable construction of high-density SNP and expression microarrays. This allowed us to further develop the conversion of the classical SNP genotyping methods (minisequencing) into more high-throughput platforms (custom SNP microarrays), which had been initiated already in the previous facilities of KTL. The in-house developed allele-specific primer

extension on microarray method was further developed to a “mini-array” format, which allowed genotyping of 5-20 selected SNPs in one multiplex with minor assay optimization requirements. Eighty samples could be analyzed at the time. In close collaboration with the Bioinfomatics core we also developed the SNPSnapper software for semi-automated genotyping of the custom SNP arrays. These in-house developed custom SNP microarrays were successfully utilized in several research projects in our laboratory and this SNP genotyping platform was also brought into play in other laboratories (University of Tampere; Haartman Institute, Helsinki; University of Uppsala, Sweden). A next step forward in the SNP genotyping pipeline was the introduction of a common quality assessment system in all the genotyping projects.

During 2002-2003 we increased the capacity in expression profiling and SNP genotyping by setting up the Affymetric GeneChip and the Sequenom MassArray platforms, which were acquired by targeted infrastructure funding (Academy of Finland, Juselius Foundation, EU, HUS EVO) and the latter was placed in the Finnish Genome Center. Full exploitation of the novel genotyping platform was enabled by implementing a large scale, partially automated DNA sample dilution and aliquoting process in 2002. This multi-step process, which utilizes Tecan Genesis 150 liquid handling automation and PicoGreen DNA quantification method, starts from the stock DNA tubes and provides quality-checked DNA in normalized concentration in 96-well format at the end. To assess the functionality of a DNA sample either a genetic tag via genotyping of a set of microsatellite markers or the gender of each sample is determined prior entering to the SNP genotyping pipeline. For low quality/low yield DNA samples a whole genome amplification protocol (WGA) was validated to complete the DNA sample pipeline. Figure 2. shows the growth of the production and the key investments in the DNA sequencing, genotyping and expression profiling pipelines during the years 2001-2006.

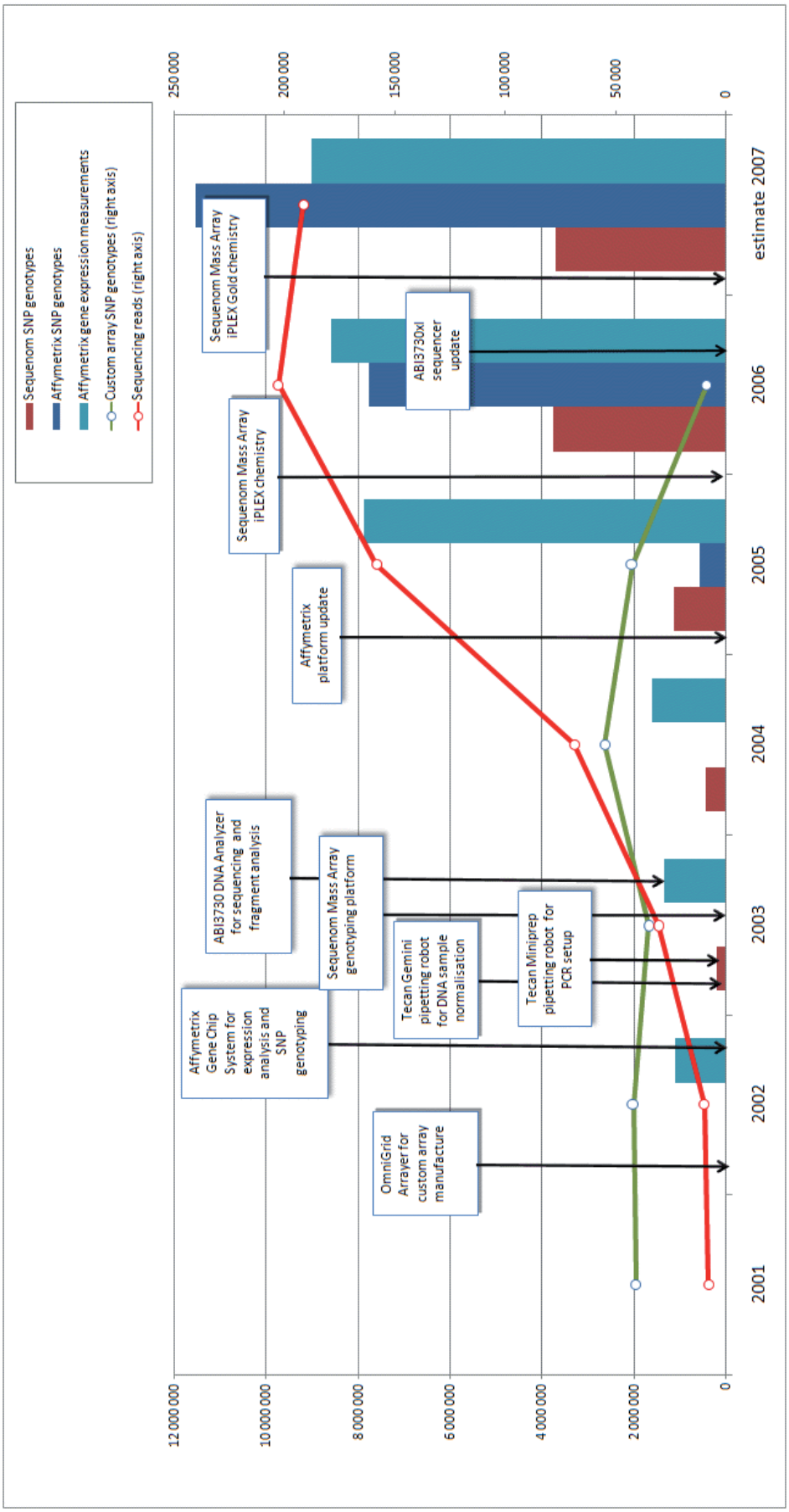

Figure 2. The growth of the production and the key investments in the DNA sequencing, genotyping and expression profiling pipelines during the years 2001-2006.

In May 2003 Molecular Medicine Sequencing Laboratory was established to rationalize DNA sequencing services in Biomedicum. A jointly funded core laboratory (University of Helsinki, Folkhälsän and KTL) enables feasible sequencing for all research groups in KTL and Biomedicum research community. Since its foundation sequencing laboratory's capacity has multiplied over the years resulting in 82 Mb of DNA sequence in 2006 (>220 000 reads of sequence). Small scale fragment analysis services are provided to complement services provided by the Finnish Genome Center.

High number of catalogued sequence variants provided by the Human Genome and the HapMap projects and the recent technical development of highly-multiplexed microarray genotyping platforms has enabled conduction of genome wide association studies. The Biotechnology core has set up majority of the currently available genome wide association panels provided by Affymetrix and Illumina and worked in close collaboration with the Genome Informatics Unit of Biomedicum to create the pipeline to efficiently store and handle the large amount of data created in these experiments. Since 2007 the core has provided mouse SNP genotyping services utilizing the Illumina SNP arrays to enable the mouse speed congenics, while management of the large genotyping projects is provided by the Finnish Genome Center/Institute of Molecular Medicine, Finland, for which the core provides technical expertise.

2.3. Scientific impact

Head of the Biotechnology core facility, Dr. Janna Saarela, operates also as a senior research scientist in projects listed under the Genetic Epidemiology research program. Thus the scientific impact is presented there based on the content.

In addition to developing microarray based SNP genotyping methods and being a primary SNP genotyping center in international collaboration studies, such as MORGAM and EURODISC, the core has organized an international workshops on SNP genotyping technologies (MORGAM workshop in Sardinia, Italy, 2004) and the representatives of the core have given lectures as an invited speakers in national and international workshops on SNP genotyping technologies and have written book chapters on the data analysis of the Affymetrix GeneChip system, SNP genotyping on microarrays and whole-genome amplification of genomic DNA. The core also participated in the Nordic quality assessment survey of SNP genotyping laboratories.

2.4. Societal impact

The research infrastructure elements like biotechnology core facility of MLO are of the critical importance for the whole research community in the modern world of biomedical research relying on the high throughput technologies and massive data production units. They can only be successful if they are guided by the needs of top research and research groups, have excellent national and international collaborations and networks and are willing to train students and scientists. The Biotechnology core of MLO is a critical element of the research infrastructure in Biomedicum and at the Meilahti campus. It educates students and researches, nationally and internationally, in the use of genome wide technologies. The core has organized or participated in the organization of the following courses:

- Genome-wide strategies in biomedical research, 2002
- Graduate School on Microarrays, 2003
- Hands-on workshop on novel biotechnology – DNA sequencing, 2005
- EMBO practical course on SNP genotyping and Haploblock analysis, 2005
- Biology for methodological scientists: Microarrays, 2006, 2007
- Biology for Methodological Scientists: Molecular Medicine, 2006, 2007
- Measurement techniques for bioinformatics – Genotyping, 2007
- EMBO Practical Course on Genome-wide SNP Association studies, 2007
- Marie Curie workshop: Array techniques to identify copy number variations, 2007

Besides, representatives of the core have given lectures on microarray based methods and their usage in studies of complex diseases, in courses and hands-on workshops organized by medical and biological faculties of Universities of Helsinki, Kuopio, Oulu and Tampere.

This core has been responsible for training all Ph.D. students utilizing the Affymetrix GeneChip system in their research projects during 2001-2003. Additionally, our core has trained most of the technicians currently working at the microarray core facility of the Helsinki region (Biomedicum Biochip Center).

2.5. Research funding

Majority of the project funding of this core comes from the specific research projects and is listed in elsewhere in this material.

Molecular Medicine Sequencing laboratory, directed by biotechnology engineer Pekka Ellonen, operates as core service laboratory thus its main funding comes from selling the services. Major instrumentation investments have been supported by infrastructure funding from KTL, University of Helsinki and HUS EVO, namely the purchase and upgrade of the ABI3730xl DNA Analyzer. The operations, QC and databases systems are being harmonized with the operations of the Finnish Genome Center as a major technology platform of FIMM.

2.6. Scientific collaboration

National

Institute	Department	Research group (PI)	Project type*
KTL - National Public Health Institute	Molecular Medicine	Prof. C.Enholm Dr. A.Jalanko Dr. M.Jauhiainen Dr. M.Kestilä Dr. V.Olkkonen Dr. T.Paunio Prof. L.Peltonen Dr. M.Perola Prof J.Taipale Dr. I.Ulmanen	SNP expr expr expr, seq expr SNP, expr, seq, custom SNP, expr, seq, custom SNP, seq expr SNP, expr, seq
	Health Promotion and Chronic Disease Prevention	Dr. V.Salomaa Dr. K.Kuulasmaa	SNP, expr SNP
	Paternity Testing Laboratory	M.Sc. M.Lukka	SNP, seq
	Infectious Disease Epidemiology	Dr. K.Liitsola	Seq
University of Helsinki	Cancer research program	Prof L.Aaltonen Prof K.Alitalo Prof M.Laiho	SNP, seq expr expr
	Public Health	Prof J.Kaprio	SNP, seq
	Molecular Medicine research program	Dr. H.Lohi Prof. A.Palotie Prof M-R.Taskinen	SNP, seq expr, seq SNP, expr, seq
	Neuroscience program	Dr. P.Tienari Prof A.Wartiovaara	SNP SNP, seq
	Forensic Medicine	Prof A.Sajantila	Seq
	Biomedicum Biochip Center	Dr O.Monni	SNP, expr
Helsinki University of Technology	Computer and Information Science	Prof. H.Mannila Prof. J.Hollmen	SNP, expr SNP, expr
Helsinki University Central Hospital	Clinical Chemistry	Dr. A.Orpana	SNP, expr, seq, custom
Haartman Institute	Virology	Prof A.Vaheri	SNP, custom
University of Tampere	Cancer Genetics	Dr. J.Schleutker	SNP
University of Oulu	Medical Biochemistry	Prof. T.Pihlajaniemi Prof. L.Ala-Kokko Dr. M.Männikkö	expr SNP SNP
	Microarray core unit	Dr J.Vuoristo	SNP, expr
University of Jyväskylä	Health Sciences	Prof. U.Kujala Prof V.Kovanen	SNP, seq expr
Finnish Food Safety Authority EVIRA		Dr M.Tikkanen	Seq

This table does not list research groups for which the unit has provided sequencing purely as service. The sequencing facility has over 60 research groups as customers.

International

Institute	Department	Research Group (PI)	Project*
University of Alberta, Canada	Faculty of Rehabilitation Medicine	Prof. T.Videman Prof. MC.Battie	SNP
University of California, Los Angeles, USA	Human Genetics	Prof. S.Nelson Prof P.Pajukanta	SNP SNP, expr
	Chemistry and Biochemistry	Prof C.Lee	SNP
McGill University, Quebec, Canada	Génome Québec Innovation Center	Prof TJ.Hudson	SNP
INSERM U525, Paris, France	Médecine Pitié-Salpêtrière	Prof. F.Cambien	SNP
Queen's University Belfast, Ireland	Epidemiology and Public Health	Prof. A.Evans	SNP
Royal College of Surgeons in Ireland	Clinical Pharmacology	Dr D.Shields	SNP
Uppsala University	Medical Sciences	Prof. A-C.Syvänen	SNP

*Projects involving mainly SNP=SNP genotyping on microarray; expr=expression profiling; seq=sequencing; custom= method development.

2.7. Proposal for the future work and expected (societal) benefits (next five years)

As the operations of the Institute of Molecular Medicine Finland (FIMM) are planned to get started in the beginning of 2008, the Sequencing laboratory will move its operations into new FIMM facilities and integrate it's operations and databases with the Finnish Genome Center (FGC). By this integration we plan to intensify the synergy in the structural analyses of genome. A major and constant challenge in genome analyses is the ever growing need of organized data storage and bioinformatics. In the FIMM environment we hope to benefit from FGC's strong IT infrastructure and tight collaboration with Genome Informatics Unit (GIU). Biotechnology core already collaborates with the FGC in several areas, including method development and QC standards, thus we are convinced that the merge will create a major infrastructure platform for FIMM and the whole biomedical research community of Finland.

A major enhancement in SeqLab's service profile is to evaluate and acquire one of the ultra-high-throughput sequencing platforms for FIMM and Biomedicum research community. Evaluation process is already well on its way and acquisition hopefully takes place during 2007. Novel technology platform will provide powerful tool for targeted re-sequencing of human genome, both deep sequencing (e.g. cancer genomics) and broad sequencing such small RNAs and expression profiling. Due to the throughput and clonal nature of novel sequencing methods SeqLab/FGC enables the FIMM and Biomedicum research community to approach their research project from new aspects thus speeding up discoveries in medicine. The core also aims to adapt new core laboratory services which fit to our profile: A good example of such methodology is Illumina Golden Gate Mouse Arrays for speed congenics, which we have adapted during 2007.

In long term plans the Biotechnology core operations aim to quickly test and adapt novel high-throughput methods needed by the surrounding research community. The means for reaching such a goal are solid networking with other professionals (researchers, bioinformatics, administration) and educating the staff to be experts in high-throughput platforms in terms of technology, process oriented thinking and cost-effectiveness. We also aim to work in close collaboration with GIU to develop methodology for data storage, handling, and analysis.

2.8. Senior personnel

Janna Saarela, MD, Ph.D., group leader
Pekka Ellonen, B Eng, laboratory manager
Kaisa Silander, Ph.D., senior scientist

2.9. References

The list does not include articles based on collaborations within the Department of Molecular Medicine, most of which are listed elsewhere in this material, based on the content of the articles.

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3 BIOINFORMATICS

3.1. Research area and its significance

Bioinformatics has become an integral and essential part of life science research gradually since its emergence in 1980's. Availability of all genome-wide data has facilitated the ongoing shift in molecular biology and molecular medicine to information based science. Accordingly the role of various interdisciplinary sciences, like bioinformatics, computational biology and biostatistics is being further emphasized. Generally no longer is molecular biology or molecular medicine performed only in the wet lab, but rather the integration of informatics techniques has become essential part of the research. In addition to the professionals in bioinformatics or in related areas, also scientists primarily working in the wet-lab are using more and more the various computational methods in their research.

3.2. The main achievements

The bioinformatics group in National Public Health Institute of Finland, Department of Molecular Medicine is the central part of an intellectual core facility, the Genome Informatics Unit GIU, www.giu.fi). The unit was established in 2002, as a collaborative project between the University of Helsinki and, Bioinformatics group and later fused with the bioinformatics group of the Finnish Genome Center, University of Helsinki in 2006. The unit is directed by Dr. Juha Saharinen (National Public Health Institute). Since the KTL bioinformatics group is integrated as part of GIU, the rest of this evaluation report covers the acts of the whole GIU.

The purpose of GIU is to provide scientific biocomputing expertise, high-performance computing resources and availability and own development of bioinformatics databases and software for researchers. The focus areas of GIU are sequence analysis, gene expression analysis, genomic annotations as well as genetic linkage and association analysis.

Currently GIU has about 650 users from the different non-profit research organizations from University of Helsinki, KTL, other Finnish universities and non-profit organizations as well as from abroad. By measurement of the number users, GIU is by far the largest academic bioinformatics establishment in Finland. In addition, GIU is not acting just a bioinformatics oriented computational service provider, rather all the personnel in GIU are actively involved in various collaborative projects, requiring expertise in bioinformatics data analysis as well as in development of applications, algorithms and relational database structures for analysis and storage of biological data.

***High-performance computing Infrastructure*:** GIU has its own high-performance computing instrumentation, including Linux cluster, enterprise scale relational database servers, storage networks, terminal server farm etc. The annual CPU capacity usage is about 60 CPU years, corresponding to about 3.8 million Cray MP CPU hours per year, putting GIU as the most used bioinformatics computing center in Finland.

Bioinformatics software and database development: GIU has made several bioinformatics applications and databases, which are used either in GIU own research, amongst GIU users, or in other universities in Finland and abroad. These applications

include enterprise scale relational database management systems for genetics and functional genomics data, namely including (see www.giu.fi/Core/Databaseandsoftwareprojects/tabid/73/Default.aspx for more complete list): GLIMS - complete laboratory information management system for genetic/genotyping laboratories; WebSaman - sample management and tracking LIMS system for high-volume laboratories ("BioBanks"); GenoFeno – genetic data: genotype, phenotype, pedigree and sample management system; GenoMart – high-volume whole genome association genotype and phenotype data warehouse (https://genomart.gu.fi); CanGEM – gene expression, aCGH and LOH database and data mining warehouse (www.cangem.org) as well as numerous other bioinformatics data management systems. Further GIU has been in a central role of multi-national scale data federation projects, where we have developed the database infrastructure, user interfaces, data federation concept as well as secured VPN connections for partnering centers to deposit, extract and analyze federated genetic data. These projects include the GenomEUtwin and Nordic Center of Excellence in Disease Genetics (see www.giu.fi/Core/Internationalcollaboration/tabid/80/Default.aspx) for more complete list). In addition to the bioinformatics databases and software developed in GIU, we provide our users the largest collection in Finland of the publicly available bioinformatics applications and databases in its focus areas and update these frequently (see https://apps.bioinfo.helsinki.fi/software/) for complete list of the public databases and software available in GIU). These allow fusion/linking of different data entities from both public as well as internal data repositories (like genotype, gene expression and molecular pathway data) and support systematic high-performance and high-throughput analysis environment. We have also developed data analysis applications utilizing this concept and used them in multiple research projects.

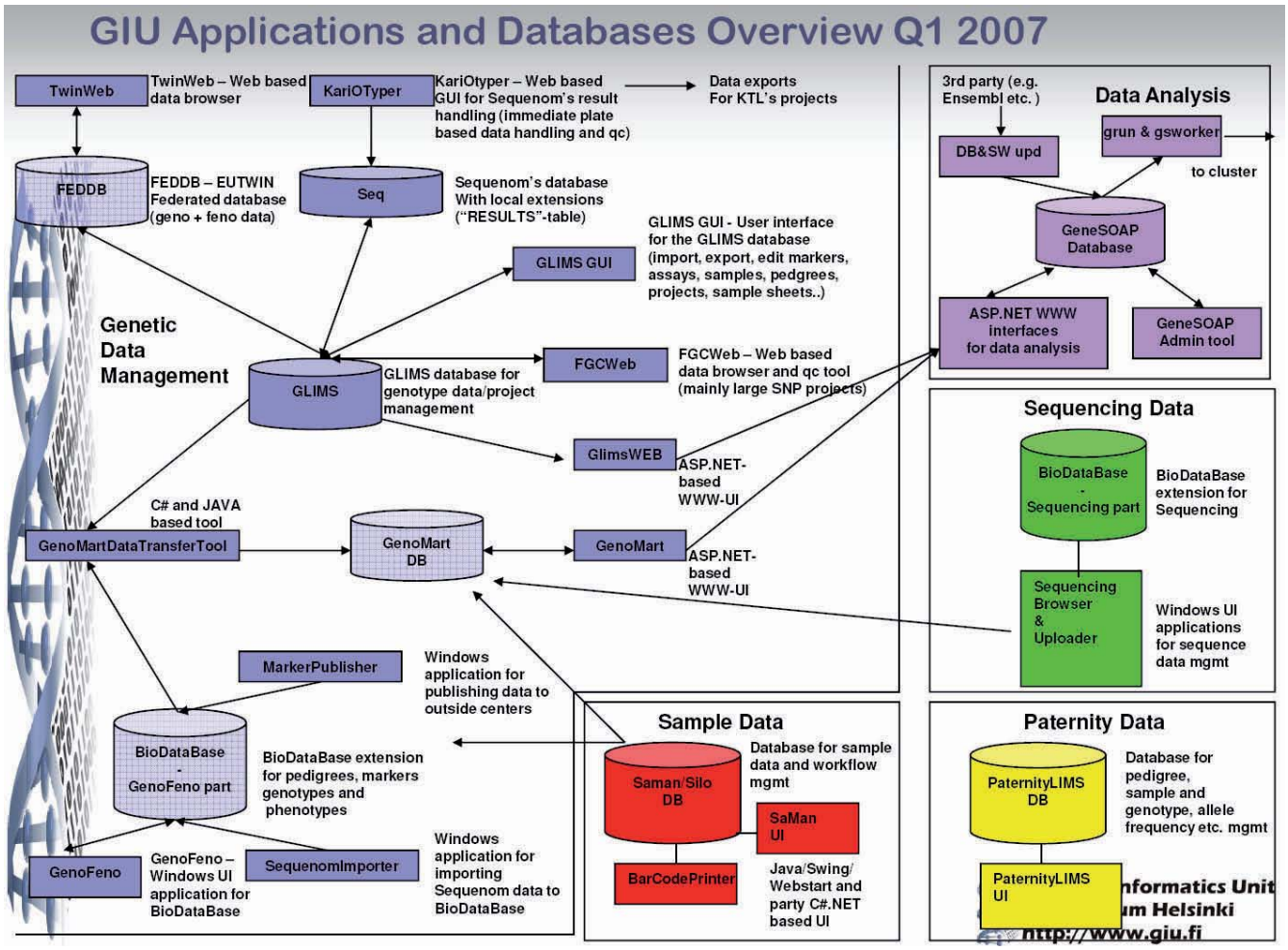

Figure 1. Major bioinformatics databases developed at GIU 2004-2007.

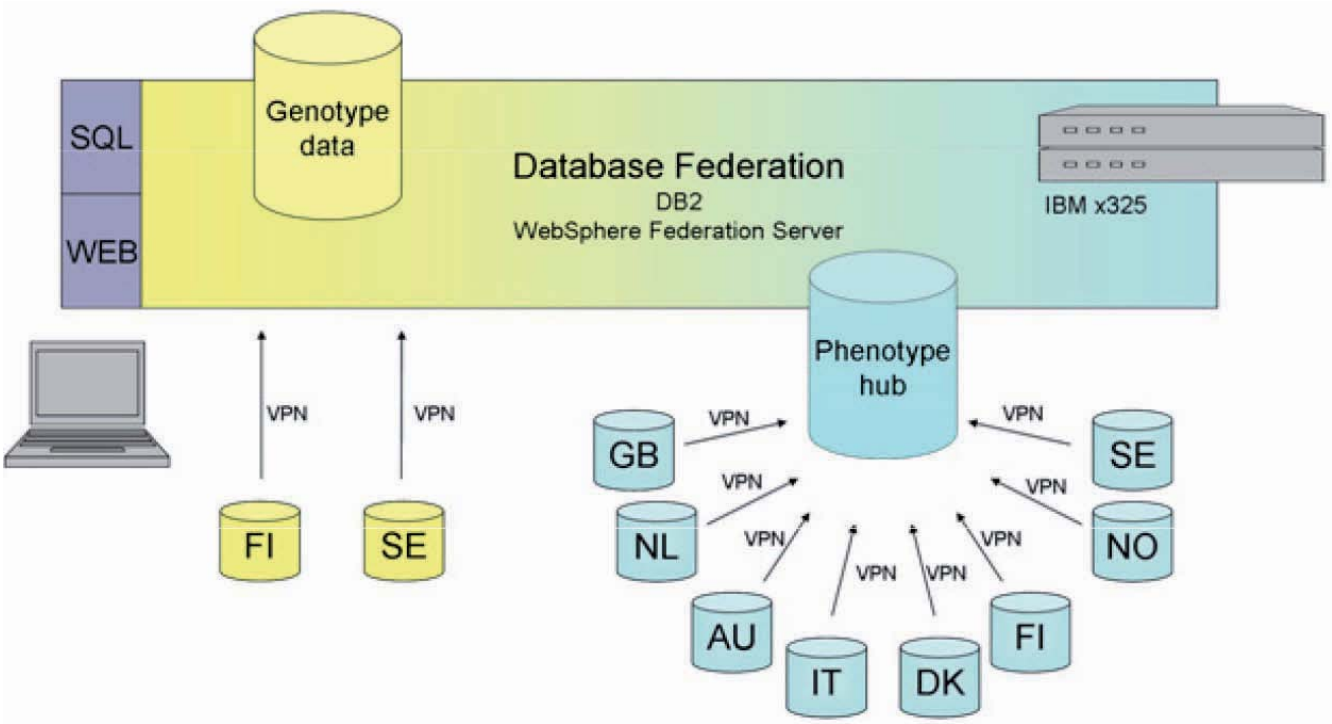

Figure 2. Bioinformatics database federation concept. The genetic data federation context, mainly developed in GIU is here illustrated as it is implemented in the GenomEUtwin project. The participating centers in different countries share their part of the data, which is federated via the data hub located in GIU, allowing all the participating centers to have a secured and controlled access to the data.

3.3. Scientific impact

The scientific impact of GIU can be categorized into three sections: 1) bioinformatics research originated/developed in GIU, 2) collaborative bioinformatics, statistical data analysis and data mining for research projects originated in other research groups and 3) teaching and advice on usage of bioinformatics, statistical and data mining tools, algorithms and databases.

We have been collaborating in numerous studies providing expertise bioinformatics, statistics and data mining methods. Our primary focus areas have been in analysis of functional genomics and genetics data. Many of these projects are mentioned in the section 3.6. Scientific collaboration. In addition to collaboration/inclusion of authorship, we have been doing a lot of advising on how to design experiments and analyze the data, in cases where the researchers are able to self learn and conduct the data analysis and allowing the scientific personnel in GIU to focus on more demanding data analysis tasks.

Another aspect of scientific impact involves teaching of the bioinformatics methods and resources. We have organized two extensive graduate student courses annually, one focusing on gene expression data analysis and the other on bioinformatics databases and data resources. In addition, we have organized each year a number of short term courses on various aspects of bioinformatics and high-performance computing related topics.

The bioinformatics research originating mainly in GIU is a more nascent area and is to be increased in the future. Our research topics are in general based around the more efficient analysis of various high performance/high volume data sets, typically in a manner that is made possible by the strength of GIU of having also the high-performance computing, software and database development and repositories within the group in addition to the scientific research interest.

Here are listed the major scientific software applications developed in GIU during 2004-2007 and excluding all *GIU Core* applications (i.e. non-scientific bioinformatics database and software).

Name: **CanGEM** Authors: Ilari Scheinin, Juha Saharinen
Status: In full production use
Home page: www.cangem.org
Description: CanGEM is a database service for storing detailed clinical information about tumor samples and microarray data. Main emphasis is on data mining studies. CanGEM is composed of custom made database/datawarehouse and a www interface partially using the latest Web 2.0/AJAX technologies alleviating most of the limits of traditional www application interfaces. CanGEM can store gene expression, array CGH/copy number, sample and phenotype data as well as experimental protocol data from a variety of microarray platforms (Affymetrix, Agilent, cDNA arrays). CanGEM includes proper authentication and access rights management system, providing users with different access levels to different projects.

Name: **LocusExpression** Author: Juha Saharinen
Status: In production use and under further development
Home page: None at the moment
Description: LocusExpression is a genome-wide gene expression data analysis method/application for finding locus/loci of genes indicating coordinated expression regulation, deviating from a permuted empirical expression. The genes of a given locus may all need not to be regulated, LocusExpression is able to find any significant partial expression regulation patterns composed of combination of genes in the given locus. Also the genes may not need to have significant expression regulation p-values as individual genes. LocusExpression is a Linux command line application, utilizing the high performance computing power and genome databases publicly available at GIU. Thus far LocusExpression method has been successfully used in one submitted publication.

Name: **ExpressionPathways** Author: Juha Saharinen
Status: In production use and under further development
Home page: None at the moment
Description: ExpressionPathways is a genome wide gene expression data analysis method/application for identifying coordinately regulated biological associations of genes ("pathways"). The genes of a given pathway may all need not to be regulated, ExpressionPathways is able to find any significant partial expression regulation patterns composed of combination of genes in the given pathway. Also the genes may not need to have significant expression regulation p-values as individual genes. ExpressionPathways is a Linux command line application, utilizing the high performance computing power and genome databases publicly available at GIU. ExpressionPathways method has been successfully used in several published or submitted publications.

Name: **WGAPathways** Authors: Juha Saharinen
Status: In late gamma-testing phase, estimated to be at version 1.0 level by end of Q2/2007
Home page: None at the moment
Description: WGAPathways is a genome wide SNP genotype association data analysis method/application for identifying coordinately regulated biological associations of genes ("pathways") sharing association signal. The genes of a given pathway may all need not to be regulated, WGAPathways is able to find any significant partial expression regulation patterns composed of combination of genes in the given pathway. Also the SNP markers may not need to have significant association p-values as individual markers. WGAPathways is a Linux command line application, utilizing the high performance computing power and genome databases publicly available at GIU. WGAPathways method is under testing in five different WGA datasets for complex diseases.

Name: **gwtf** Authors: Tommi Ripatti, Juha Saharinen
Status: In late beta-testing phase, under statistical performance evaluation
Home page: None at the moment
Description: Traditionally prediction of transcription factor binding sites form sequence, regulating gene expression has been immensely difficult task, producing typically ~10-fold false positive rate. Recent addition of using comparative genomics (phylogenetic footprinting) has increased the performance significantly, but still we are far from a robust and reliable method. Gwtf is an attempt to utilize other than linear sequence information for TFBS prediction, namely benefitting from spatial signals in the DNA/predicted TFBSes in addition to comparative genomics information. This and other information is then analyzed by machine learning methods, both by supervised and un-supervised manner, in an attempt to produce more reliable TFBS predictions which then are used to predict meaningful rSNPs. Some parts of gwtf system have been used in a published paper.

Name: **GeneSOAP** Authors: Juha Saharinen, Teemu Perheentupa
Status: In late public gamma-testing phase
Home page: www.giu.fi/Default.aspx?tabid=215
Description: GeneSOAP provides a web services interface for execution of tens to hundreds of different bioinformatics applications and databases. GeneSOAP can distribute the execution of the applications to e.g. various servers/clusters in different institutions, providing a GRID middleware functionality. GeneSOAP provides a standard and secured WebServices/SOAP interface, usable in any modern programming language (Perl, Python, Java, C#, VB, Ruby, C++ etc.) as well as command line interface, native Windows graphical client and www interface (BioPortal).

Name: **AffySNP** Author: Juha Saharinen
Status: In full production use
Home page: None at the moment.
Description: AffySNP is a program for handling Affymetrix WGA SNP genotyping data to be further analyzed for linkage multipoint lod scores in pedigrees with inbreeding loops.

Name: **CartoGrapher** Authors: Juha Knuuttila, Juha Saharinen
Status: In full production use and under statistical testing for improvements
Home page: www.giu.fi/Default.aspx?tabid=118
Description: A properly-ordered marker map is essential for successful linkage analyses. Existing genetic marker maps have been shown to be inconsistent with the actual genome sequence, and manual construction of maps is time consuming and error prone. To solve this

problem, we have developed Cartographer, a method that automatically builds a physically-ordered marker map, generated from a list of marker names, using the localization of full-marker and marker-primer sequence data. Cartographer is provided also with a web interface in BioPortal (https://apps.bioinfo.helsinki.fi/software/cartographer.aspx

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Name: **MPD – Multiplex Primer Designer** Author: Juha Saharinen
Status: In full production use
Home page: www.giu.fi/Default.aspx?tabid=199
Description: Multiplex primer designer (MPD) is a program for designing primers for multiplexed PCR reactions such as multiplexed SNP genotyping assays. MPD designs PCR assays avoiding annealing of primers to the other products in the multiplexed reaction. MPD screens the generated primers for homology against other sequences within the multiplexed assay and rejects high homology candidates. In addition, Multiplex primer designer will use a Primer3 repeat masking library to prevent primer design within repeated genomic regions. Currently a human specific repeat library is used. MPD is provided also with a web interface in BioPortal (https://apps.bioinfo.helsinki.fi/software/mpd.aspx

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Name: **siRNA designer** Author: Juha Saharinen
Status: In full production use
Home page: None at the moment
Description: siRNA designer is a method/application for designing optimal siRNA/shRNA gene silencing targets/oligos. siRNA designer is based around the latest information of thermodynamic asymmetry in RNA strand specificity of RISC complex loading as well as a large number of experimentally deduced heuristical rules for optimal siRNA/shRNA targets. In addition, siRNA designer adds to the model the most probabilistic RNS secondary structure information, aiming to target siRNA/shRNA oligos to regions of low RNA strand dublex occupancy. Further, siRNA designer validates the uniqueness of the candidate probes by sequence level homology searches against target organism specific cDNA sequences. siRNA has been compared to other known siRNA/shRNA design tools/methods and successfully used in number of projects, including the Helsinki Biocentrum Systems Biology Initiative for making a library of hundreds-to-thousands siRNA/shRNA silencing constructs.

Name: **SNPSnapper** Author: Juha Saharinen
Status: In full production use
Home page: www.giu.fi/dnn/Default.aspx?tabid=179
Description: SNPSnapper is a software package developed to produce accurate allele calling and genotyping of samples from custom SNP microarray data in semi-high-throughput genotyping facility. The raw data obtained from a microarray canner, containing intensity values of the localized spots, is first read and sorted according to SNPs and genotyped persons. Allelic pairs of each SNP for a given person are then sought and different graphical representations are drawn based on calculated data from the allelic pairs, in which the sample pairs are shown as dots. The allelic calls/genotypes assignments are done semi-automatically using unsupervised machine learning algorithm, possibly further tuned by the user. SNPSnapper is backed up by a custom made relational database for a LIMSS system containing experiments, projects, chips, subjects genotypes, array designs etc. and includes proper authentication and access rights management system, providing users with different access levels to different projects. SNP-Snapper is in production use in multiples genotyping laboratories in many countries.

3.4. Societal impact

Courses

A significant part of the GIU efforts are devoted to educating the scientific society in key areas of bioinformatics, covering how to analyse data acquired through genome-wide technologies, e.g. expression and SNP microarrays, and how to use biological information from public repositories (biodatabases), to yield more biologically relevant interpretation of the data. This is achieved by organising courses, seminars and one-on-one consultations for scientists in, or associated with, research groups in Biomedicum. Courses are either organised on our own initiative, requested by researchers in need of tutoring in topics related to bioinformatics or arranged on behalf of other educational organisations.

Courses organised on behalf of Helsinki Biomedical Graduate School, include the following:

- Practical Bioinformatics - Microarray data processing, analysis and management, 2006
- Practical Bioinformatics - Biodatabases, 2006
- Practical Bioinformatics - Microarray data analysis, 2007
- Practical Bioinformatics - Biodatabases, 2007

Courses organised on our own initiative, or by specific request from researchers, include the following:

- Using GeneSpring for analysis of microarray data - basics, 2005
- Using GeneSpring for analysis of microarray data - advanced, 2005
- Using BRB Array Tools for microarray data analysis, 2005
- Crash-course in basic microarray data analysis for Biomedicum researchers, 2006
- Crash-course in basic microarray data analysis for NPHI/MLO researchers (29.9.2006)
- Basic databases and SQL for Bioinformatics, 2007

In addition to the above courses usually taught at class-room scale, a wealth of smaller scale courses, or tutorials, instructing researchers how to use the numerous bioinformatics tools developed by GIU have been given on request. Guidance in issues related to the analysis of large scale data sets as well as how to incorporate information from biodatabases into the analysis and/or the interpretation of the results have also been given to satisfy specific needs of research groups.

GIU staff is also involved in teaching during courses organised by other organisations. Examples of this are the following courses given by the Finnish Centre for Scientific Computing (CSC);

- GeneSpring basic course, 2003
- GeneSpring basic course, 2006

Impact on national bioinformatics ecosystem

GIU provides several services nationally for life science researchers that are unique in Finland. These include various genetic data handling solutions (GenoMart, GenoFeno, CliniFeno etc. systems), computational resources (HPC Linux cluster, enterprise scale database servers, MS Windows server farm etc.) as well as collaboration on scientific projects.

In the very near future, GIU is planning too opening its bioinformatics database services to be openly accessibly directly from any Finnish research organization, without the need to log in to GIU system and thus being easier to integrate into institutes' own data analysis pipelines. Further GIU will open its BioPortal WWW service for hundreds of bioinformatics applications and databases for open use (currently available for testing at https://apps.bioinfo.helsinki.fi/software).

Collaboration in international bioinformatics service projects

GIU has been actively collaborating and working with data integration systems and standards for genetic research. The work has been done in international research programs and consortiums like P3g (www.p3gconsortium.org), GenomEUtwin (www.genomeutwin.org), NCoEDG (www.ncoedg.org) and the PML (www.openpml.org).

The data integration system developed for the GenomEUtwin project allows to federate data directly from seven twin centres using secure distributed database techniques. Currently the system provides access for phenotypic data of over 200 000 twins. In addition to GenomEUtwin, the GIUs expertice in data integration systems and standards are also used in other projects like Nordic Centre of Excellence in Disease Genetics and Centre of Excellence in Academy of Finland. GIU is also participating in multiple applications submitted for the 7th EU framework. The applications, sent as bids for six different calls, are related database and data integration systems and standards for molecular epidemiological studies, biobanking and medical genomics.

GIU is also the home for public and open CanGEM (cancer genome mining) –database (www.cangem.org), which is developed in GIU. CanGEM is an integrative, systems biology oriented database for array CGH and gene expression data of cancer samples, bound to various international ontologies (eVOC, WHO ICD-10, TNM). Currently CanGEM contains data from about 1,500 samples.

3.5. Funding

About 90% of both the personnel and computer instrumentation and maintenance funding of GIU is coming from competitive research sources. The annual salary sum is about 600 000€ and the annual expense of the instrumentation is about 200 000€, as averaged over the five year period of GIU's existence.

Due to the nature of a substantial proportion of GIU being a high-performance computer and scientific software and database development unit, and thus not completely devoted to science, this is a quite problematic situation. In order to acknowledge the established and proven status of GIU as a bioinformatics and statistical computing unit, our suggestion would be that National Public Health Institute provide similar level of funding for the infrastructure part of GIU as it is providing the administrative ICT and data management units in KTL, and thus only the research persons in GIU would be funded from the research grants. This would also have a great impact on the quality of service in GIU due to adequate sever maintenance agreements and more predictable budget for renewal and upgrade of the instrumentation.

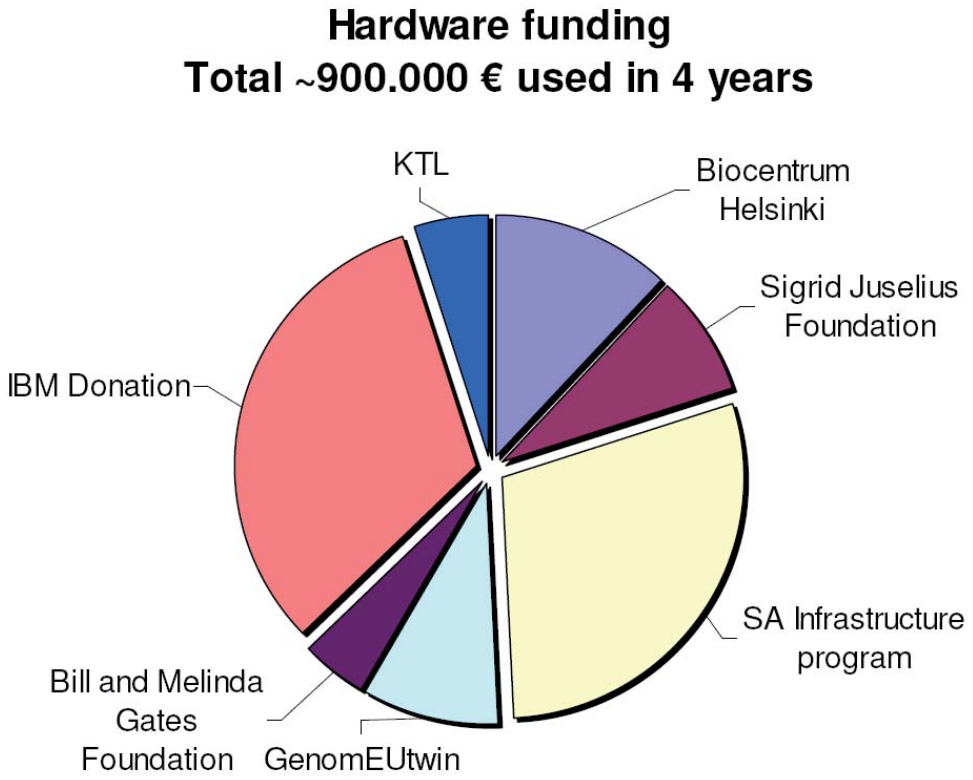

Figure 3. Funding of the high-performance computing instrumentation in GIU. About 85% of the funding has come from competitive sources.

3.6. Scientific collaboration

This list covers the list of scientific collaborations have taken place during 2003-2007.

Global transcript profiles and pathways of adipose tissue in weight-discordant monozygotic twin pairs. Prof. A.Rissanen, Dr. M.Oresic, Prof. H.Yki-Järvinen, Prof. J.Kaprio, Prof. L.Peltonen (University of Helsinki, Helsinki University Central Hospital, KTL, VTT Technical Research Centre of Finland)

Transcript profiles of brain in Cln1 and Cln5 deficient mice. Dr. A.Jalanko, Prof. L.Peltonen (University of Helsinki, KTL)

Activating mutations in colorectal adenocarcinomas. Prof. L.Aaltonen (University of Helsinki)

Comparative genomics analysis of genomic landscape and gene expression in vertebrates. Prof. H.Mannila, Prof. L.Peltonen (University of Helsinki, KTL, HIIT Helsinki Institute for Information Technology)

Transcript profiles and pathways of dendritic cells of PLOSL patients link demyelinating CNS disorders. Prof. I.Julkunen, Prof. L.Peltonen (University of Helsinki, KTL)

The federated database - a basis for biobank-based post-genome studies, integrating phenome and genome data. Prof. L.Peltonen, Prof. JE.Litton (University of Helsinki, KTL, Karolinska Institutet, Sweden)

Indicative oligodendrocyte dysfunction in spinal cords of human fetuses suffering from a lethal motoneuron disease. Dr. M.Kestilä, Prof. L.Peltonen, Prof. H.Sariola, Dr. K.Wartiovaara (University of Helsinki, KTL)

Gene expression and copy number profiling in asbestos-associated lung cancer. Dr. H.Wikman, Prof. J.Hollmen, Prof. S.Knuutila, Prof. S.Anttila (University of Helsinki)

Infantile onset spinocerebellar ataxia caused by mitochondrial proteins Twinkle and Twinky. Prof. L.Peltonen, Prof. A.Suomalainen (University of Helsinki, KTL)

Transcriptomal profiling of human lymphatic endothelial cells. Prof. K.Alitalo, Prof. D.Kerjaschki (University of Helsinki, University of Vienna, Austria)

Cellular pathways and DNA copy number changes in primary uterine leiomyosarcoma. Dr. T.Böhling, Prof. S.Knuuttila (University of Helsinki, Helsinki University Central Hospital)

Profiling genetic variation along the androgen biosynthesis and metabolism pathways in prostate cancer. Dr. J.Schleutker, Prof. O.Kallioniemi, Prof. M.Vihinen (University of Tampere, VTT Technical Research Centre of Finland)

Batten disease (JNCL) linked to disturbances in mitochondrial, cytoskeletal, and synaptic compartments. Dr. A.Jalanko, Prof. L.Peltonen (University of Helsinki, KTL)

Pathways regulating cell size and cell-cycle progression. Prof. J.Taipale (University of Helsinki, KTL)

Cross-species analyses in human glucose metabolism. Prof. J.Kaprio, Prof. A.Rissanen, Prof. V.Salomaa, Prof. K.Kontula, Prof. MR.Taskinen, Prof. P.Pajukanta, Prof. L.Peltonen (University of Helsinki, Helsinki University Central Hospital, KTL, University of California, Los Angeles, USA)

USF1 and dyslipidemias. Prof. P.Pajukanta, Prof. MR.Taskinen, Prof. L.Peltonen (University of Helsinki, Helsinki University Central Hospital, KTL, University of California, Los Angeles, USA)

3.7. Proposal for the future work and expected (social) benefits (next five years)

Together with the establishment of the Finnish Institute for Molecular Medicine (FIMM) and integration of the Department of Molecular Medicine into FIMM the national role of GIU as a research oriented bioinformatics unit will be further emphasized and tentatively supported by increase of both personnel as well as computing hardware capacity.

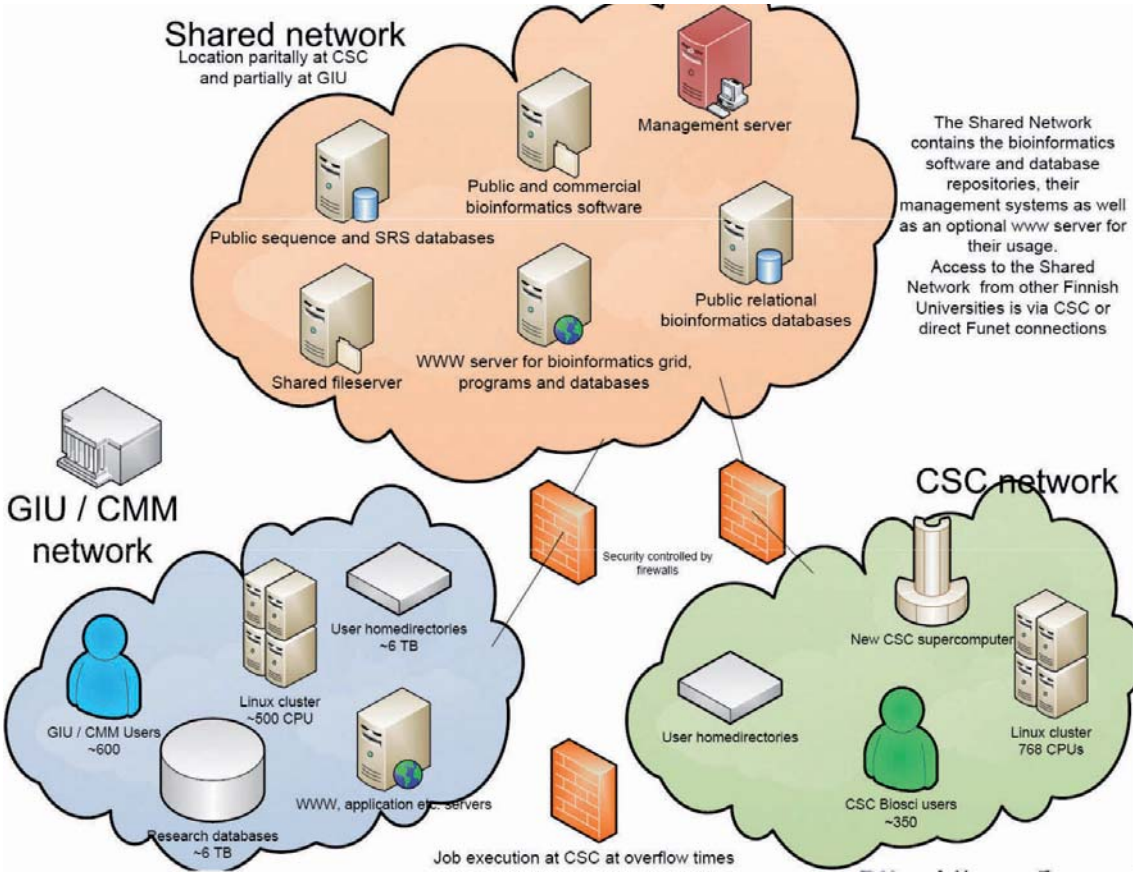

Figure 4. National access of the GIU bioinformatics database and software repositories. The goal is to build national system for access of the resources in GIU and allowing direct connections to these from all the Finnish Biocenters, in a way that supports systematic, high-performance and high-throughput analysis. CSC (National supercomputing resource in Finland) is planned to provide the peak computing capacity for most CPU intensive data analysis.

3.8. Personnel

The personnel involved in GIU comprise postdoctoral and graduate level researchers, system administrators as well as students, emphasizing the role of GIU as an educational entity. The background education of the employees varies including biochemistry, computer science, mathematics and civil engineering. The co localization of the bioinformatics unit in the same building with the traditional wet lab laboratories has proven to be a key issue for a successful collaboration between the two disciplines and emphasized the status of bioinformatics being a cross-disciplinary field of science.

Currently GIU employs 15 persons, 10 of them with the competitive external funding. The division of the GIU personnel into Infrastructure, Core (bioinformatics software and database development and management) and Science in depicted in Figure 5.

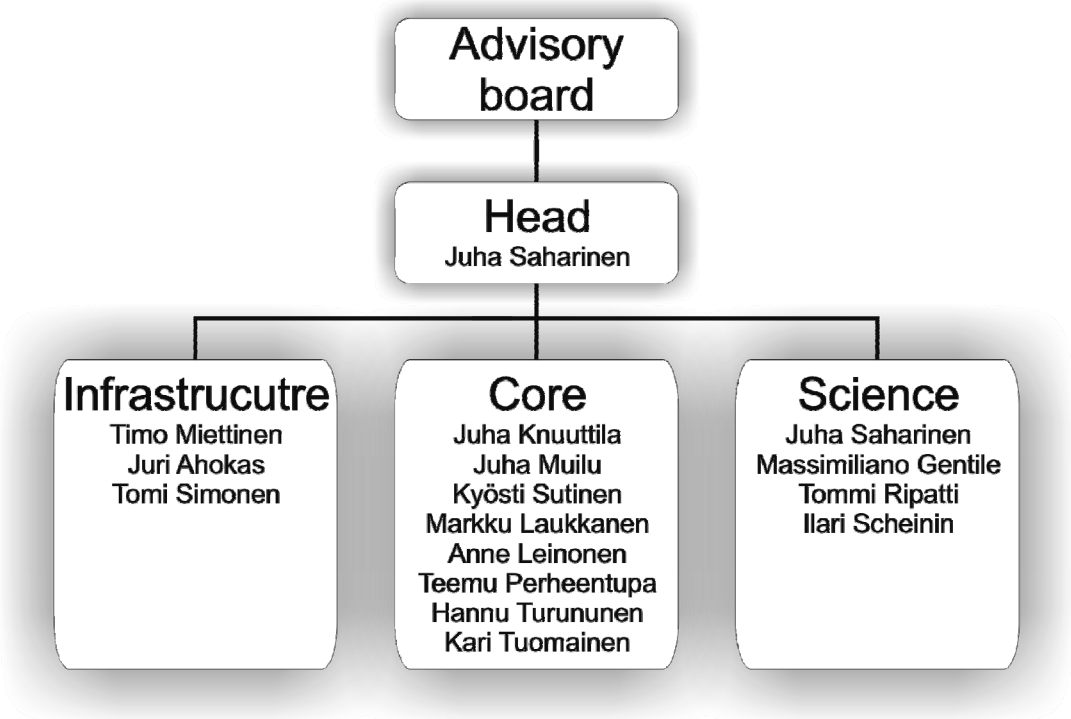

Figure 5. Structure and personnel in GIU.

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4 Large Scale DNA Extraction and Storage Facility National Biobank of Finland

4.1. Background

Numerous global efforts have been launched recently to establish biobanks. The word 'biobank' is a little over a decade old. The first record in PubMed of its use appears in 1996. A biobank has recently been defined by OECD as "a collection of biological material and the associated data and information stored in an organised system for a population or a large subset of a population". KTL biobanking effort is older than most biobanks and importantly has been founded based on the epidemiological data collections. Already in early 1980s the large ATBC study had a strong biological sample arm and since 1990 all the epidemiological data collections of KTL have been accompanied by the systematic collection of biological samples, serum, plasma, blood for DNA extractions and biomarker determinations. MLO has been the centralized site for DNA and RNA extraction, storage, aliquoting and logistics for all KTL study samples. However, while individual collections can be well organised and accessible, there remains a need to harmonise between them by establishing networks. There also remains a need to ensure the longevity of the resources through appropriate funding mechanisms. Further, the DNA extraction and logistics laboratory has become a national site for biobanking materials, it holds numerous other large cohorts samples, including all the twin cohort samples and all Finnish birth cohorts samples (www.nationalbiobanks.fi). During past 10 years the KTL biobanking laboratory has also become the international DNA logistics site being in charge for DNA extraction and logistics for numerous EU funded studies.

In the KTL biotechnology strategy biobanking was recognized as a key element for the future success of KTL. At the European level, many MLO investigators played a key role in biobanking-related discussions of the European Strategy Forum on Research Infrastructures (ESFRI) comprises representatives of EU Member States and Associated States and a representative of the European Commission. Its role is to support a coherent approach to policy-making on research infrastructures in Europe, and to act as an incubator for international negotiations about concrete initiatives. In 2006 its Roadmap for pan-European research infrastructure development across the sciences was published and then formally received by the Commission. ESFRI's decision to include infrastructure to underpin research in the life sciences is significant because it indicates that there is for the first time a general recognition that the scale of life science research endeavours has increased to a point where separate research groups and various biobanking efforts need to pool resources. Europe's national health care systems have facilitated collection of clinical samples and produced highly reliable health care records. Furthermore, Europe has strengths in epidemiological studies that have, over decades, accumulated data complemented often by biological samples. The diversity of European populations with well established but different histories is a beneficial feature for various research strategies. New biobanking initiatives have been launched and just like the older biobanks, they all rely on these strengths. The ministry of social and health affairs supported this effort as one of the major Finnish ESFRI initiatives and MLO investigators were in the critical position in producing the BBMRI bid for the

ESFRI call of FP7. MLO houses the website of BBMRI and Dr. Peltonen is the chair of the governance board of BBMRI (www.biobanks.eu).

When the first DNA extraction facility was initiated in KTL in 1990, the DNA was extracted manually, and sample information was stored mainly by researchers working in distinct projects. As the number of collected samples increased yearly there was a growing need for centralized DNA extraction core unit; permanent staff, and automated DNA extraction and aliquoting machinery. During the evaluation period 1997-2007 the number of the staff has increased from two laboratory technicians to 11 persons. Autopure DNA extraction robot was purchased in 2001 and Tecan aliquoting robot in 2002. The functioning of the unit has evolved from a DNA extraction laboratory into a coordinated biobank. The need for a large-scale DNA logistics facility in KTL has originally arisen from the needs of scientists working with large sample collections and this need still clearly exists. From the very early start we have seen the synergy of the Core working in close interaction with both the clinicians collecting the samples as well as geneticians utilizing the DNA in their studies. This has been a very fruitful approach ensuring both that the Core key personnel is closely following the front-line of genomic science and also realizes the importance of flexibility and rapid response to changing requests from biobank users. Accordingly, due to its good track record and the trust in our professional approach, the Core has been selected as the DNA biobank for several large international projects, funded by EU, pharma and different governmental and private entities.

We have during the years of operation evaluated several commercially available database systems for the facility. However, after careful consideration, we have decided to develop the database interfaces in-house to ensure the flexibility and data protection needed in this kind of large cross-departmental facility. The database system of the facility works as a web - client to web - server connection to SQL server 2005 database. The web - client uses newest AJAX functionality offered by Microsoft to enable smooth UI. All operations to database are logged into transaction log, so it is possible to see what modifications have been done by whom. All operations can be rolled back using internal transaction handling mechanism. The sample receive, DNA extraction and DNA dilution are all combined to single web - client. There is large number of checks to make it possible to check to logical content of DB in any moment.

4.2. Functioning of the unit and the main achievements

Currently the biobank houses over 200 000 DNA samples, and some hundreds of RNA- and protein samples. Emphasis of the biobank is in DNA extraction, quality control and logistics. In 2006 over 15 000 DNA samples were extracted, and over 45 000 DNA aliquots were distributed to researchers worldwide. In addition to extraction and aliquoting robotics the facility is equipped with a state of the art bar coding system for sample tracking and confidentiality, and a tailor made database, SamWise, for data management, the full control of logistics, and on-line monitoring of the sample processing.

The facility is responsible for sample management in several national and international research projects. The biggest national projects are Finrisk-studies (-87, -92, -97, -02, -

07; approximately 60 000 DNA samples), Health2000 (15 000 DNA samples), and Finnish Twin cohort (over 13 000 DNA samples). The major international projects are EU-projects GenomEUTwin and Genetics of Healthy Ageing (GEHA) and the International MORGAM study. Except these large population cohorts, the unit also handles the DNA logistics or various study samples ascertained for major diseases like cardiovascular diseases, schizophrenia or autism.

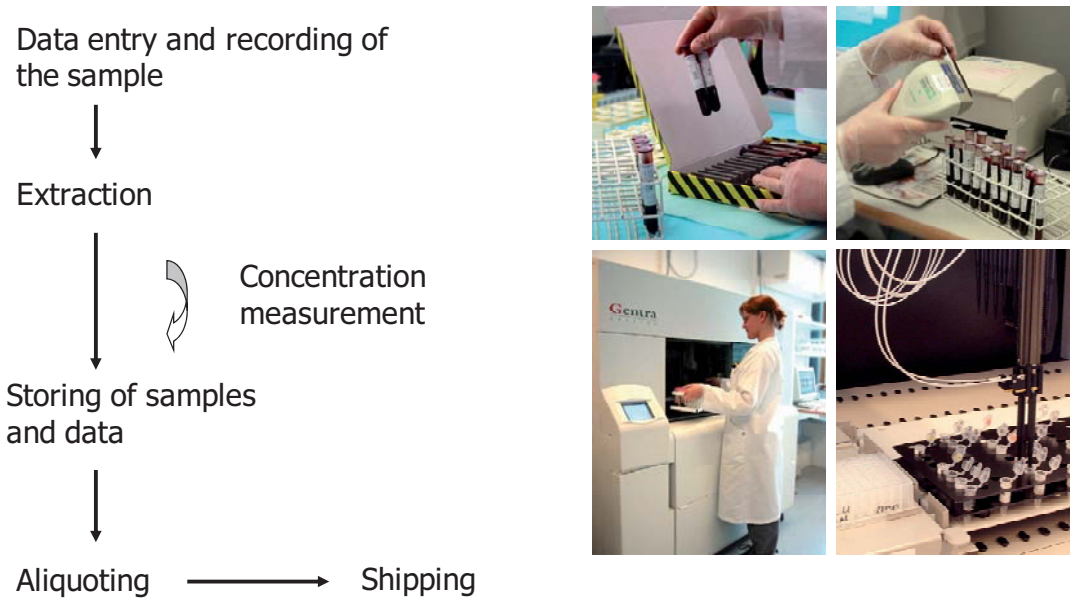

Figure 1. Handling of samples in the DNA isolation process

4.3. Scientific and societal impact

Human biological samples including associated medical data, and biomolecular research tools are a key resource in unravelling the interplay of genetic and environmental factors causing diseases and impact on their outcome, identification of new targets for therapy and reduction of attrition in drug discovery and development. The Finnish national biobanking effort has already biological samples from over 4% of the population and thanks to the KTL's position as the national health monitoring authority, the linking of epidemiological data and vast amount of data collected via the national health care system with the information produced from biological samples is exceptionally feasible. KTL can build on existing sample collections, resources, technologies, and expertise, which is increasingly complemented with innovative components of the use of genome wide tools and properly embedded into Finnish scientific, ethical, legal and societal framework. The scientific impact of the Finnish biobank has already proven to be high, most of the frequently cited publications of MLO and KTL have been produced based on the biobank samples. Further, several EU grants have been obtained thanks to this centralized, well organized effort of MLO.

Finally, most large scale national efforts in molecular epidemiology as well as the European BBMRI are heavily dependent on the sustainability and continuity of this national biobanking resource and the database and analytical structure integrated with it.

4.4. Funding

About 60% of the funding comes from the governmental budget covering salaries of technicians and a laboratory manager. The salaries of a project manager and another laboratory manager are paid by the competitive external funding (20% of total budget). Profits from services cover the rest of the funding, total budget being about 500 000€. About 35% of the budget is used for supplies and equipments.

4.5. Scientific collaboration

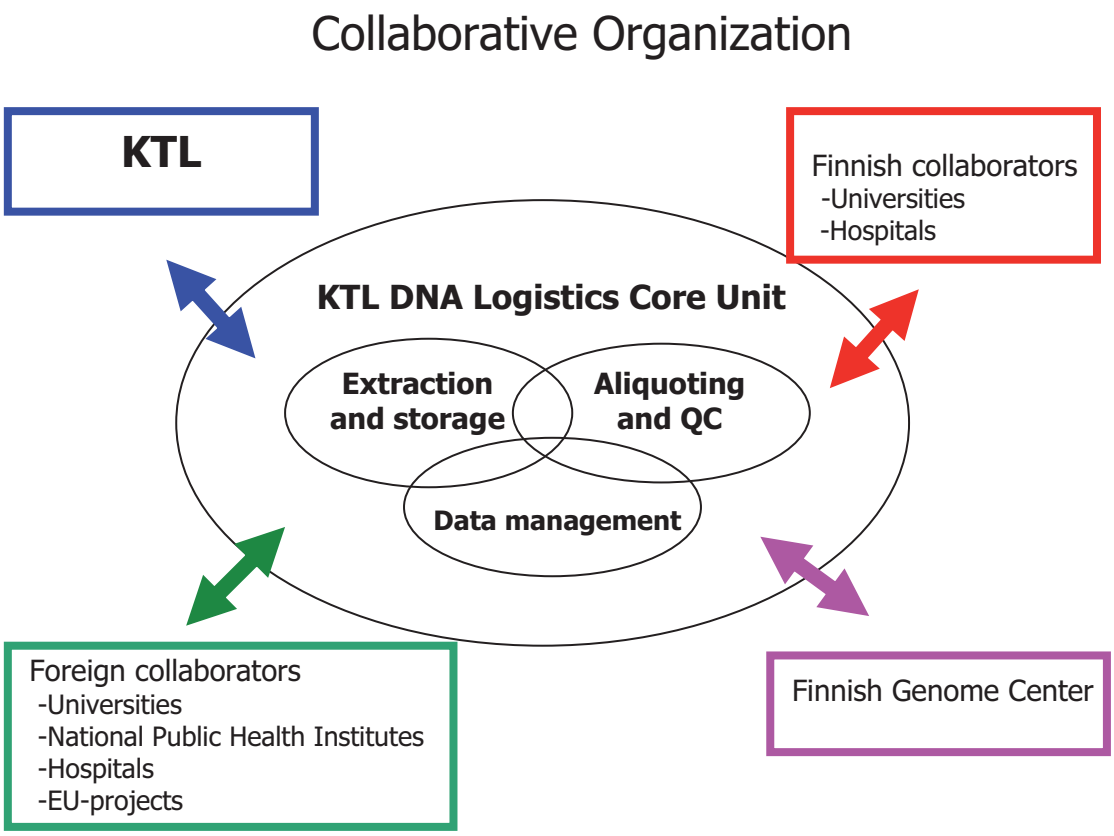

Figure 2. Collaborations of DNA extraction and storage facility/National Biobank of Finland

4.6. Proposal for the future work and expected (social) benefits (next five years)

The facility plans to stay in the fore-front of modern sample management. This will be a necessity given the large and significant international responsibilities taken up by us. We are key members in large EU-funded projects, such as GenomEUtwin, GEHA and

ENGAGE, in which especially the sample management issues have been dedicated to us. The facility personnel frequently visit the partner laboratories and groups to exchange ideas and experiences and takes also part in scientific meetings of the projects, when seen necessary or useful. We are also a member of P3G and ISBER-organizations and regularly participate in their meetings to get up-to-date information and share our experiences in modern sample management. The facility will be a Core Unit in the newly founded FIMM and clearly a necessity for the Institute to meet its mission. The greatest challenges in future are in keeping up with the increasing need for rapid large-scale extraction and aliquotting of specific sample sets. This challenge will be faced with increasing automation of the facility and continuing development of the database tools in house.

4.7. Personnel

The facility has a highly qualified staff of a project manager (Päivi Laiho, Ph.D.), two laboratory managers (Outi Törnwall, M.Sc., Minttu Jussila, M.Sc.) for DNA extraction and aliquoting logistics, and eight laboratory technicians. In 2006, KTL/MLO recruited the expert in biobank-related societal and ethical issues, Professor Helena Kääriäinen, to emphasize the critical importance of the societal impact of this national effort.

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5 FINNISH DISEASE HERITAGE

5.1. Research area and its significance

In the beginning of 70's a concept of the Finnish disease heritage (FDH, www.findis.org) was introduced by Jaakko Perheentupa and colleagues. Today FDH consists of 36 distinct monogenic disorders (Figure 1.), which are more common in Finland than in other countries. The reason for this enrichment is thought to be the founder effect/population bottlenecks, inbreeding and the relative isolation of Finnish population, because of linguistic, geopolitical and geographical reasons.

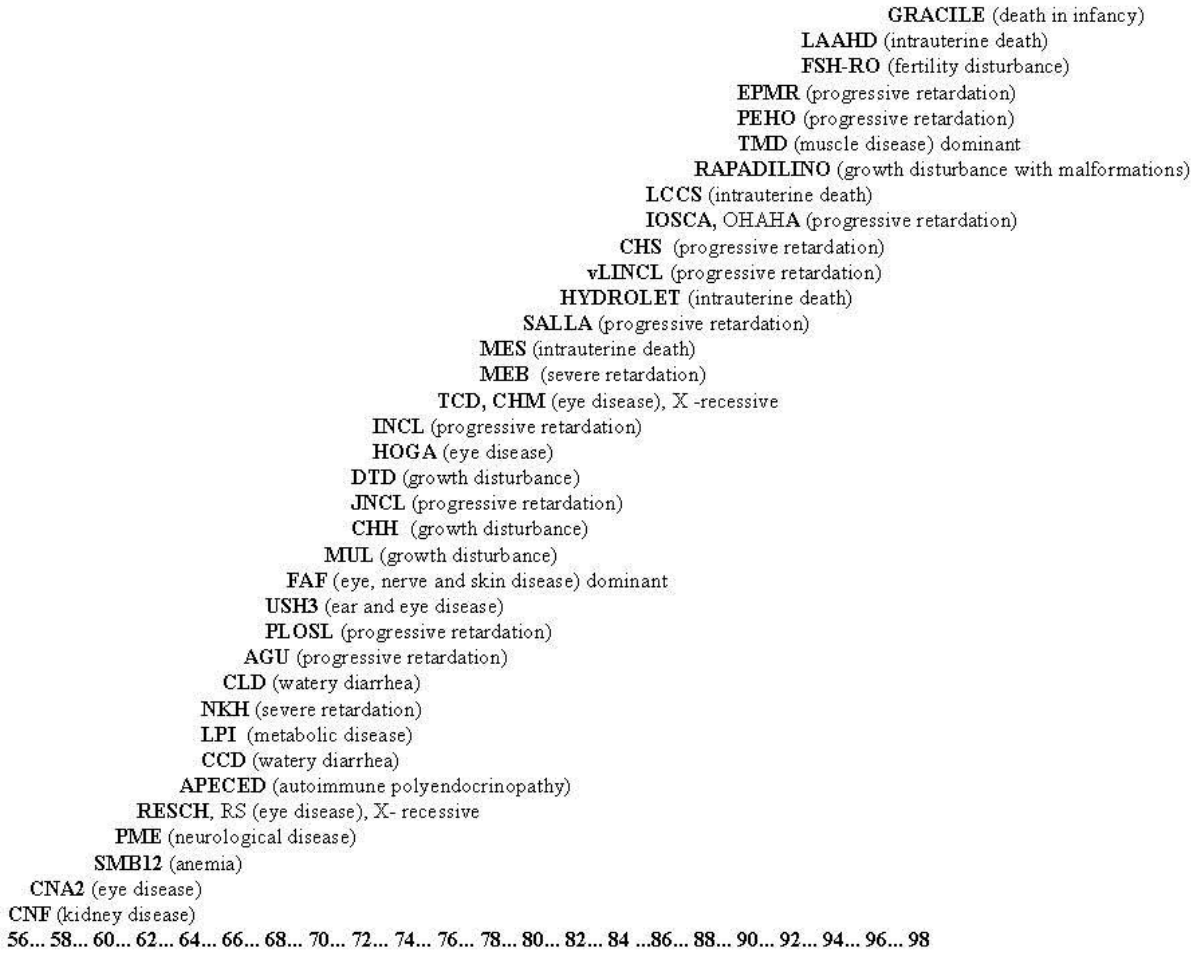

Figure 1. Diseases of the Finnish disease heritage presented as so called Perheentupa's steps. The vertical line shows the year when the phenotype was published for the first time.

The search for the disease-causing genes started in the 1980's. Some of the disease genes were characterized based on the knowledge about of a known protein that was found to be defective in a disease. However, this kind of information was not available in most disorders and different approach was needed.

In the end of 1980's Leena Peltonen and co-workers started to search for FDH genes by positional cloning. This is the method of choice to find the gene when the molecular pathogenesis of a disease is unknown. Initially, a locus was localized to a specific

chromosomal region by linkage analysis in families. Next the critical DNA-region was restricted by using linkage disequilibrium and monitoring for a shared haplotype among affected individuals. Finally regional candidate genes were analyzed in order to identify the disease-causing mutations.

In general, the study of monogenic diseases has provided most valuable information on the molecular pathology of diseases, on the basic consequences of different mutations, as well as on the identification of the physiological functions of human genes. Furthermore, identification of the disease causing genes and respective proteins, have opened avenues to understand novel metabolic pathways and exposed new potential causative genes.

The detection of the specific mutations has provided molecular tools for the diagnostics of FDH diseases. Consequently gene and mutation specific diagnostic methods have been developed and they are in use for prenatal and postnatal diagnostics. In principle, the high throughput methods developed for screening of the FDH disease mutations would enable us to effectively screen for the mutation carriers. We have tested a chip with 19 disease mutations in the random sample of Finnish population and established carrier frequencies varying regionally from 1:6-1:12 for all mutations. Perhaps even more importantly, identification of a disease gene has created also an excellent tool to study molecular and cell biology of the diseases, the final goal, yet mostly to be achieved, being the understanding of pathogenesis of a disease. In future, this information enables us to plan novel therapeutic approaches for FDH and other monogenic diseases, based on new potential therapeutic target molecules.

Current investigations have revealed that there is not any clearcut difference between monogenic and complex polygenic diseases. Firstly, in a setting of Finland, representing a founder population molded by multiple bottlenecks, methods like homozygosity mapping or haplotype sharing combined with GWA genotyping platforms can be used to identify rare alleles of common disease loci facilitating shorcuts to genes, not identifiable by Hapmap-based GWA strategies. Consequently, the knowledge and paradigms of the Finnish population structure, established in the study of FDH diseases can be applied effectively for the efforts to expose and functionally analyse the allelic variants behind complex traits.

5.2. The main achievements

Genetics

At the moment 35 FDH genes have been characterized. Nineteen of these have been identified and/or studied at the Department of Molecular Medicine (previously the Department of Human Molecular Genetics) in the National Public Health Institute or in the collaboration with MLO researchers (Table 1.). Our efforts in understanding the molecular genetics of the FDH genes have revealed the major mutation(s) as well as other minor mutations in the Finnish population as well as in some other populations. The geographical distribution of the disease alleles in Finland has indicated that this is the consequence of the population history and the age of the founder mutation of the disease.

Table 1. FDH genes that have been identified and/or studied at the Department of Molecular Medicine or in the collaboration with MLO researchers. Diseases marked in bold are discussed in more detail in this report.

Disease [OMIM number]	**Defective protein/gene**	**Fin-major mutation and its' percentage value in Finnish patients**
Amyloidosis V [105120] (dominant)	Gelsolin (*GSN*)	D187N, 100%
Aspartylglucosaminuria (AGU) [208400]	Aspartylglucosaminidase (*AGA*)	C163S, 98%
Autoimmune polyendocrino-pathycandidiasis ectodermal dystrophy (APECED) [240300]	Autoimmune regulator (*AIRE*)	R257X, 82%
Juveline neuronal ceroid lipofuscinosis (JNCL) [204200]	Novel transmembrane protein (*CLN3*)	Genomic deletion of 1.02 kb, 90%
Congenital lactase deficiency (CLD) [223000]	Lactase gene (*LCT*)	Y1390X, 90%
Congenital nephrotic syndrome of the Finnish type (CNF) [256300]	Nephrin (*NPHS1*)	c.121_122delCT (L41fs), 78%
Free sialic acid storage disease (Salla disease) [604369]	Solute carrier family 17, member 5 (*SLC17A5*)	R39C, 95%
Growth retardation, aminoaciduria, cholestasis, iron overload lactacidosis and early death (GRACILE) [603358]	BCS1-like (*BCS1L*)	S78G, 100%
Hydrolethalus syndrome (HLS) [236680]	Novel protein with unknown function (*HYLS1*)	D211G, 100%
Infantile neuronal ceroidlipofuscinosis (INCL) [256730]	Palmitoyl protein thioesterase 1 (*PPT1*)	R122W, 98%
Infantile onset spinocerebellar ataxia (IOSCA) [271245]	Twinkle protein, mitochondrial precursor (*PEO1*)	Y508C, 99%
Lethal arthrogyposis with anterior horn cell disease (LAAHD)	Gene identified, not yet published	Mutation identified, not yet published
Lethal congenital contracture syndrome (LCCS) [253310]	Gene identified, not yet published	Mutation identified, not yet published
Meckel syndrome (MKS1) [249000]	Novel cilia protein (*MKS1*)	IVS15-7_35del (P470fs), 100%*
Northern epilepsy (EPMR) [600143]	Novel TM protein (*CLN8*)	R24G, 100%
Polycystic lipomembranous osteodysplasia with sclerosing leuko-encephalopathy (PLOSL) [221770]	TYRO protein tyrosine kinase-binding protein (*TYROBP*) and Triggering receptor expressed in myeloid cells-2 *(TREM2*)	Genomic deletion of 5.2 kb, 100%**
RAPADILINO syndrome [266280]	RecQ protein-like 4 (*RECQL4*)	IVS7+2delT resulting in a in-frame skipping of exon 7, 85%
Tibial muscle dystrophy (TMD) [600334] (dominant)	Titin (*TTN*)	11 bp insertion/deletion resulting in a change of four amino acids, 100%
Variant late infantile neuronal ceroid-lipofuscinosis (vLINCL) [256731]	Novel soluble/TM protein (*CLN5*)	Y392X, 95%

*Only about 70% of Finnish MKS-patients have a mutation in the *MKS1* gene, but all of these have the same mutation. **All Finnish PLOSL patients have the same mutation in the *TYROBP* gene, but different mutations in the *TREM2* and *TYROBP* genes have been identified from foreign PLOSL patients.

Development of strategies for analysis of gene function

Identification of a disease gene and disease-causing mutations creates an excellent tool for future studies. Most of the novel genes of the FDH were originally of unknown function and this created the need to develop tools for molecular, cellular and tissue analyses for the characterization of gene function and disease mechanisms. Figure 2. illustrates the general outline of the strategy used to study the diseases the goal being to understand molecular pathogenesis of a disease. This approach has been successfully utilized for several genes of the FDH and the methodological expertise is currently being transferred for the analysis of gene function in complex diseases.

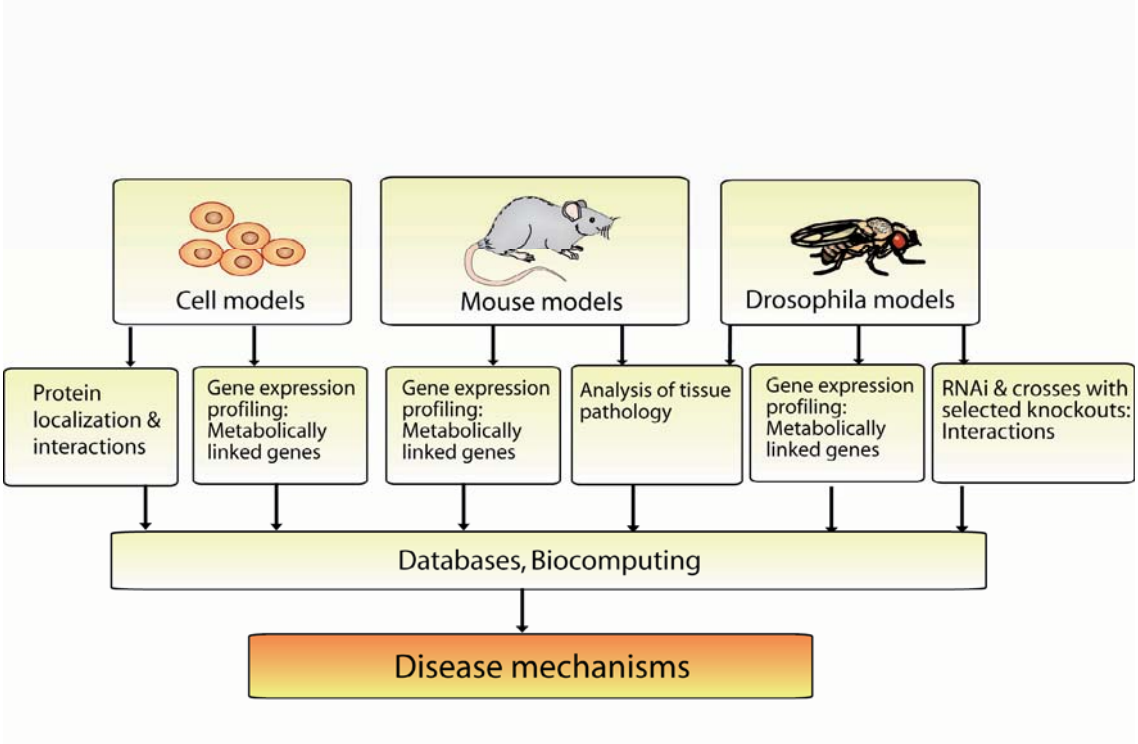

Figure 2. Approaches to study pathogenesis of an inherited disease

The research program of Finnish Disease Heritage has utilized different cellular models to analyze the intracellular localization, transport of normal and mutant disease proteins and these studies have brought us novel information about molecular functions of general importance. For example, in the case of Aspartylglucosaminuria, we could show the whole spectrum of analyses from gene characterization and cellular studies to protein crystallization, identification of a novel activation mechanism and determination of a phosphotransferase binding site for lysosomal targeting of the Aspartylglucosaminidase.

In order to facilitate the initial characterization of exposed new pathways and to analyze the consequences of the gene elimination at organism level, we have produced knock-out (KO) mouse models for six FDH and utilized a total of nine FDH mouse models (Table 2.), most of which have already been characterized in detail by us. The post-genomics era has introduced demands to investigate and characterize the global variation evident within biological systems and we have routinely utilized transcript profiling to expose disturbed molecular pathways in our mouse models. Additionally, other systematic analysis methods are under development or utilized in collaborative

efforts. Importantly, the department has had the resources and excellent collaboration partners to conduct functional analyses based on findings form the genome-wide analyses, for example neurological dysfunction in the NCL and immunological functions in the APECED mouse models. In the case of the AGU mice, several therapeutic interventions have also been applied. The major findings based on the studies of the mouse models utilized by MLO are summarized in Table 3.

Table 2. Mouse models at the Department of Molecular Medicine*

Disease	**Gene**	**Main phenotype**
Infantile neuronal ceroidlipofuscinosis (INCL)	Palmitoyl Protein Thioesterase 1 (*Ppt1)*	Early onset thalamocortical atrophy Blindness at 3-4 months Motor abnormalities Early death at 5-6 months
Juveline neuronal ceroidlipofuscinosis (JNCL)**	Novel transmembrane protein (*Cln3)*	Late onset thalamocortical atrophy Retinal degeneration White matter abnormalities Mild neurological phenotype Death at 18 months
Variant late infantile neuronal ceroidlipofuscinosis (vLINCL)	Novel soluble/TM protein (*Cln5)*	Early onset reverse thalamocortical atrophy Blindness Motor abnormalities Early aging Death at 8-10 months
Northern epilepsy (EPMR)**	Novel TM protein (*Cln8*)	Late onset thalamocortical atrophy Retinal and motor degeneration Spastic paralysis Death at 10-12 months
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)	Autoimmune regulator (*Aire)*	Mild autoimmune symptoms Autoantibodies, reduced fertility
Growth retardation, aminoaciduria, cholestasis, iron overload lactacidosis and early death (GRACILE)	Bcs1-like (*Bcs1l*)	Not determined
Aspartylglucosaminuria (AGU)	Aspartylglucosaminidase (*Aga*)	Thalamic atrophy Mild motor abnormalities
Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL)**	TYRO protein tyrosine kinase-binding protein (*Tyrobp*) and Triggering receptor expressed in myeloid cells 2 (*Trem2*)	Thalamic atrophy Cortical changes Mild motor and sensory defects Not determined

*In addition, two KO mouse models are under the process of microinjection (Meckel syndrome and hydrolethalus). **These models were not initially produced by us but inbred into C57/BL congenic background.

Neuronal ceroid lipofuscinoses (INCL, vLINCL, JNCL, EPMR)

The neuronal ceroid lipofuscinoses (NCLs) represent the most frequent group of inherited neurodegenerative diseases in children. These rare diseases, caused by mutations in eight known genes, provide a unique model to characterize the molecular pathways critical for normal neuronal development and involved in neurodegeneration. The research group of Peltonen has provided essential information by identification of two disease genes behind INCL (*CLN1, PPT1*) and vLINCL$_{Fin}$ (*CLN5*) and contributing to the mapping/identification of genes behind JNCL (*CLN3*) and variant LINCL (*CLN6*). Groups Peltonen and Jalanko were in the key position in the analyses of the cellular localization of four NCL proteins PPT1, CLN3, CLN5 and CLN8, involved in the infantile, variant late infantile and juvenile NCLs and demonstrated that all of these except CLN8 are lysosomally located in non-neuronal cells. We have identified a considerable number of mutations resulting in these disorders and usually the disease mutations cause defects in the transport of these NCL proteins. The mRNA expression patterns of three NCL genes in mouse brain have been characterized and implicate important roles for CLN1, CLN3 and CLN5 in neuronal development. We have further analyzed the neuronal localization of PPT1, CLN3 and CLN8 proteins and showed that these proteins possess distinct properties in neurons. Additionally, we have defined novel targeting sequences and transport mechanisms of CLN3 protein.

We have also provided the first clues to the functions of the NCL proteins in mammalian cells. PPT1 and CLN3 deficiencies were shown to be linked to endocytic abnormalities. For the CLN3 protein we have demonstrated interconnections with the microtubule-associated protein HOOK1 and CLN3 deficiency was shown to be linked to deregulated cytoskeletal function. To reveal the functional roles of NCL-proteins, we have systematically screened interaction partners for PPT1, CLN3 and CLN5 proteins. Our most recent unpublished findings show that PPT1 interacts with the F1 complex of ATP synthase and this interaction mediates neuronal lipid homeostasis. Additionally, we have revealed interactions between CLN3, and the cytoskeleton-related proteins fodrin, Na,K,ATPase and Grp78/BIP and shown that CLN3 participates in the endocytosis of the sodium pump. We have further identified novel interactions of CLN5 protein with PPT1, CLN2, CLN3 and CLN6, implicating that CLN5 is a central player in a common NCL pathway. The molecular interactions of NCL proteins are summarized in Figure 3.

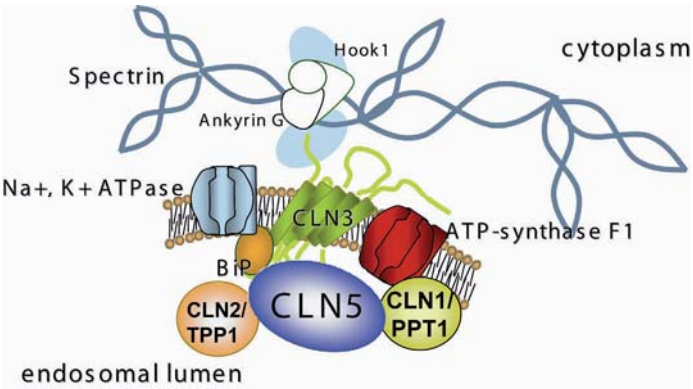

Figure 3. NCL protein interactions

MLO investigators have produced KO mouse models mimicking human NCL mutations and they are in a good position to use these rare human diseases to characterize molecular pathways behind the associated neuronal degeneration. Each NCL mouse model exhibits a progressive NCL-like neurodegenerative phenotype that resembles the corresponding human disorder and these models are proving a valuable resource for understanding how the brain is affected. The mouse models of NCL display a selective neuronal loss early in pathogenesis with localized astrocytosis and neuronal loss in the thalamocortical system, detectable by quantitative immunohistochemical analyses and MRI. The *Cln5*$^{-/-}$ mice show distinct properties by exhibiting a "corticothalamic" neuron loss, first observed very early in cortex and only subsequently within the thalamus. In the context of the EU consortium NCL models, coordinated by A. Jalanko, we have backcrossed the *Cln1/Ppt1*$^{\Delta ex4}$, *Cln3, Cln5* and *Cln8/mnd* mouse models into the C57Bl6 genetic background. This will make the NCL mouse models an invaluable source for the research community.

We have utilized global transcript profiling to expose dysregulated pathways in NCL mouse models and demonstrated that *Cln3* deficient cortical neurons exhibit disturbances in mitochondrial, cytoskeletal and synaptic functions and similar analysis of *Cln1* deficient cortical neurons revealed dysregulated lipid homeostasis, substantiated by biochemical measurements. We have also performed transcript profiling for the cortices of 1 and 4 month old *Cln1* and *Cln5* models and analysed these data comparatively to reveal a common affected pathway involving the neuronal cytoskeleton and growth cone assembly. The production of the congenic mouse strains for five NCL disorders has opened a new avenue to explore and compare affected pathways in NCL. We have initiated comparative global analyses utilising transcript and lipid profiling in four mouse models of NCL and aim at further understanding of the NCL biology.

Autoimmune polyendocrinopathycandidiasis-ectodermal dystrophy (APECED)

Autoimmune disease APECED is another example of the value of detailed characterization of a rare FDH diseases, which has exposed a novel and fundamental biological pathway by providing fundamental pieces of information to understand the mechanisms of immunological tolerance and autoimmunity in general. After reporting the locus for APECED in Finnish families, our laboratory and a Japanese group independently in the same issue of Nature Genetics 1997 reported the causative gene *AIRE.* We have subsequently chracterized the functional defects of patient mutations resulting in the increased understanding of the domains of the AIRE protein and their functions. We have used yeast two-hybrid assay to identify nuclear proteins which interact with AIRE protein. Most interesting finding was the interaction of AIRE with PIAS proteins PIAS1, PIASxα and PIAS3, representing E3 SUMO ligase proteins. We have studied in detail the cellular and functional consequences of the AIRE-PIAS1 interaction. These results implied that this interaction was able to modulate transcription in gene specific fashion, linking AIRE transcription regulation with the SUMO-pathways.

Furthermore our group was the first one to construct and characterize *Aire* KO-mouse, which have been intensively used by us and in collaborations to reveal the central role of AIRE in the regulation of gene expression in thymus medullary epithelial cells. These studies have established the importance of AIRE in the development and maintenance of central tolerance. By comparing the immunological properties of the mouse model and APECED patients we could demonstrate that that the immunopathology in the two

organisms was far from identical. Thus for instance the functionality of regulatory T cells was impaired in patients but not in knock-out mice. Furthermore, the pattern of autoantibodies was mostly different. These results complied nicely with the observation that our mouse model displayed generally much milder autoimmune symptoms than APECED patients. The important conclusion was that results obtained from the mouse model should be critically applied for man. Further studies are in progress to reveal the role of AIRE in peripheral tolerance. Figure 4. illustrates important milestones of our APECED research project at MLO.

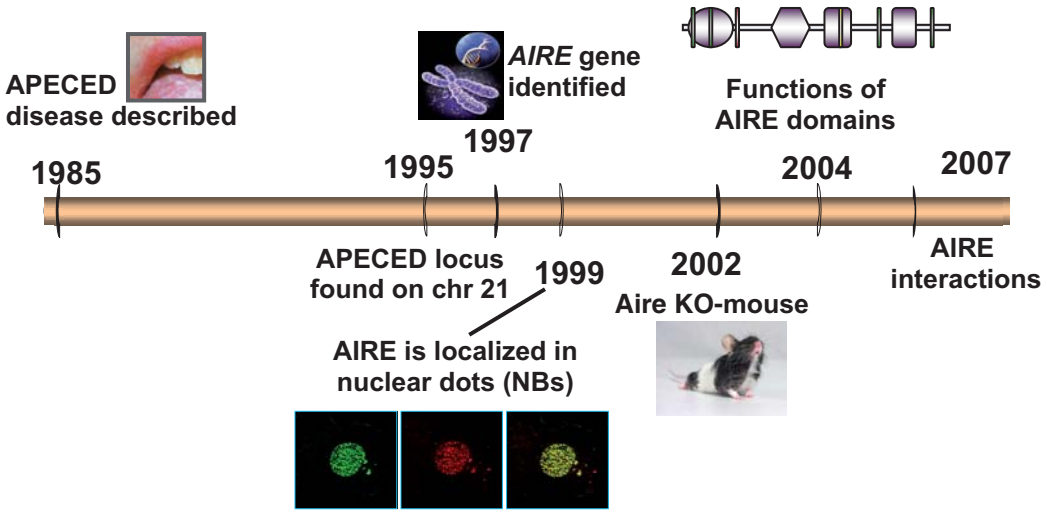

Figure 4. The most important milestones in the APECED research project

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL)

PLOSL, also known as Nasu-Hakola disease, is a recessively inherited disease characterized by combination of osteoporosis and early-onset progressive dementia. This disease has been considered of special interest as a monogenic model of dementia with complex phenotype. We have characterized the molecular background of PLOSL by identifying mutations in two genes, namely *TYROBP* and *TREM2*, implicating that the same disease can be caused by mutations both in the ligand and receptor of an immunomodulating complex. The disease phenotype is identical regardless of which one of the genes is mutated. Interestingly, patients with PLOSL do not clinically manifest immunological defects, but the symptoms appear in brain and bone and the function of TYROBP and TREM2 have remained elusive in these tissues.

TYROBP functions as a transmembrane adapter protein, which plays an important role in myeloid and natural killer (NK) cell activation and thus in triggering and amplifying inflammatory responses. TYROBP interacts with many different receptors depending on the cell type and together with TREM2 they are known to promote survival of human dendritic cells. We have shown that also microglial cells in the brain and osteoclasts in the bone, both target cells of the PLOSL, express the TYROBP/TREM2 receptor complex. More recently we have utilized global transcript profiling of dendritic cells of PLOSL patients and demonstrated dysregulation of actin bundling and immune response pathways. The pathological cascade induced by the lack of TYROBP/TREM2

is likely to trigger an inflammatory response in the CNS and our recent studies have implicated the importance of oligodendroglial cells in this event (Kiialainen, unpublished). To obtain deeper insight into the CNS pathology in TYROBP/TREM2 deficiency, we have recently produced a TREM2 knockout mouse and aim to utilize it together with the existing TYROBP KO-mouse for further studies involving the interplay of TYROBP and TREM2 in the CNS.

Lethal fetal syndromes (HLS, MKS, LCCS, LAAHD)

The most recent studies of FDH have been focused to early birth defects enriched in Finland with the hypothesis that these rare diseases might contribute to our understanding of critical molecular pathways guiding human development. During the first year of life birth defects are the leading cause of death. These defects are defined as abnormalities of structure, function or body metabolism that are present at birth resulting in physical or mental disability or death. Birth defects can be caused by genetic or environmental factors, but in many cases reasons remain unknown. Four of the FDH diseases cause very severe birth defects that lead to death already in utero or immediately after birth. These syndromes - Meckel syndrome (MKS), Hydrolethalus syndrome (HLS), Lethal Congenital Contracture Syndrome (LCCS) and Lethal Arthrogryposis with Anterior Horn cell Disease (LAAHD) - will create shortcuts to the identification of new molecular mechanisms and events providing clues to understanding of organogenesis, dysmorphogenesis and human malformations generally.

Meckel syndrome (MKS) represents the most common form of syndromic neural tube defects (NTDs). Main symptoms are polycystic kidneys, occipital meningoencephalocele, fibrotic changes of the liver and polydactyly. MKS is diagnosed worldwide and it is a heterogenous disorder; two genes (*MKS1* and *MKS3*) and one locus (MKS2) are known, but these findings explain only a part of the MKS cases. We have recently characterized a novel *MKS1* gene and a major mutation (29 bp intronic deletion) that has been found from 70% of Finnish MKS cases and from several Caucasian patients. We are currently searching for additional MKS loci using Finnish patients without mutations in the *MKS1* or *MKS3* genes or linkage to MKS2 locus. The comparative genomics in *Chlamydomonas*, *Arabidopsis* and human strongly support the role of MKS1 in flagellar (cilia in human) basal body proteome. Later, functional studies have shown that both MKS1 and meckelin (MKS3 protein) are linked to cilia, but the final function is not known yet. Meckel syndrome is the most severe one of known ciliopathies that is a very heterogenous group of disorders since the abnormal cilia function can be a cause for e.g. diabetes and overweight.

Hydrolethalus syndrome (HLS) was discovered in Finland in the course of studying the Meckel syndrome (MKS). Like MKS, this disorder is characterized by central nervous system malformation and polydactyly, but unlike MKS, it does not show cystic kidney and liver, and the CNS derangement is hydrocephalus with absent midline structures not encephalocele. The pregnancy is characterized by hydramnios, which is often massive. The hydrolethalus syndrome is caused by the substitution of aspartic acid by glycine in a novel protein with an unknown function. Genome-wide expression arrays have revealed up-regulation of genes related to cell cycle regulation in patient cells. Studies by cultured neuronal progenitor cells obtained from an aborted HLS fetus and from normal fetuses (from pregnancies terminated for social reasons) have also shown patient cells having an increased cell proliferation rate. To identify the pathways associated with the function of the HYLS1 protein, we have created a transgenic knock-

in *D. melanogaster* model expressing human HYLS1 and the detailed analysis of the fly model is in progress.

Lethal arthrogryposes are a genetically and clinically heterogeneous group of disorders characterized by multiple contractures at birth. Today the diagnosis is often made based on the abnormal position of joints and diminished or lack of movements of a fetus in utero. Typical examples of these syndromes are Lethal Congenital Contracture Syndrome (LCCS) and Lethal Arthrogryposis with Anterior Horn cell Disease (LAAHD). Autopsies demonstrate the hallmarks of these diseases, muscular atrophy and paucity of anterior horn motor neurons. We have very recently identified mutations that cause both LCCS and LAAHD. These diseases are allelic and there is a distinct genotype-phenotype correlation. The study of these most severe motoneuron diseases will provide valuable information about the genes and pathways essential to normal motoneuron function and insight into the molecular mechanisms behind other motoneuron diseases such as ALS.

Conclusion

Table 3. The main results/achievements of the functional studies of FDH-genes at the Department of Molecular Medicine

Cell models/ Cell phenotype	**Animal models**	**General significance**
Infantile neuronal ceroidlipofuscinosis (INCL)		
Cellular localization and molecular interactions of PPT1.	Novel features in brain pathology, functional analyses in knockout neurons. Novel metabolic pathways revealed.	First clues to synaptic involvement in NCL. Cell and animal studies show that INCL is linked to dysregulated lipid homeostasis.
Juveline neuronal ceroidlipofuscinosis (JNCL)		
Intracellular localization and molecular interactions of CLN3.	Novel metabolic pathways, functional analyses in knockout neurons.	First clues to CLN3 function in mammalian cells. JNCL linked to cytoskeleton-mediated dysregulation of ion transport.
Variant late infantile neuronal ceroidlipofuscinosis (vLINCL)		
Intracellular localization and molecular interactions of CLN5.	Novel features in brain pathology. Novel metabolic pathways revealed.	First clues to common affected pathways in NCL. CLN5 may be the central player in NCL biology.
Autoimmune polyendocrinopathycandidiasis-ectodermal dystrophy (APECED)		
Transient expression of AIRE and 13 different patient mutations.	Mechanisms of immunological tolerance.	Molecular mechanisms of central and peripheral tolerance. Cellular pathogenesis of AIRE mutations.
Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL)		
Cellular localization and functional studies of dendritic signaling	Novel metabolic pathways revealed	Connection between actin bundling and demyelination. Oligodendrocyte phenotype revealed

5.3. Scientific impact

Table 4. Summary of the scientific output during 1997-2007

Scientific output	**N**	**Comments**
Peer-review articles in international journals	165	In addition 23 review articles/book chapters. See Appendix 1
Invited lectures and chairmanships in international meetings	15	e.g. Chair - The 10th International Congress of Neuronal Ceroid Lipofuscinoses, Helsinki 2005
Articles in domestic journals and text books	5	See Appendix 1
Lectures in domestic meetings and teaching lectures	75	
Editorial tasks in international journals	1	BBA Molecular Basis of Disease 2006
Committee memberships: domestic	3	e.g. Board member of Finnish Gene Therapy Society, 1999–2005 Member
Committee memberships: international (EU, WHO etc.)	3	e.g. Member of the European Society of Gene Therapy Committee on gene therapy for genetic diseases 2000–2002
International evaluation panels (EU etc.)	2	e.g. Coordinator, EC FP6 STREP project NCL-models LSHM-CT-2003-503051, 2004-2006
Organizing committee of international meetings	5	e.g. Member of the Scientific Advisory Board: The 9th International Congress of Neuronal Ceroid Lipofuscinoses, Chicago, USA, 2003; Member of the Scientific Advisory Board: The 11th International Congress of Neuronal Ceroid Lipofuscinoses, Rochester, NY, USA, 2007
Doctoral dissertations	28	See Appendix 1
Supervision of dissertations: Ongoing	11	
Opponent of dissertations	5	
Pre-examiner of - dissertations - adjunct professors - professorships	 23 1	
Prizes	1	The best Ph.D. thesis 2006 (Kaisu Luiro), Faculty of Medicine, University of Helsinki

5.4. Societal impact

About 60 newborn babies are born every year in Finland who suffer from FDH diseases already at birth or later in their lives. Most of the FDH mutations cause very severe or even lethal disease and the situation is always very hard for the whole family. The family wants to know if the disease is inherited, is there a risk for an affected child also in future pregnancies and is there any treament. Identification of disease-causing mutations has made DNA diagnostics possible. All mutations identified at MLO are available for diagnostic testing in the HUCH Laboratory Diagnostics (Helsinki, Finland).

The mutation analysis confirms the diagnosis and the best treatment, if available, can be planned.

Charaterization of the molecular defect behind Finnish disease heritage has been a community effort linking experts in clinical medicine and genetic councelling with molecular geneticists, cell biologists and mouse experts. Total of 10 000 Finns have contributed to these studies with their biological samples and clinical data. The concept of Finnish genetics became world famous along with this national effort and this accomplishment has substantially increased the interest towards genetic research among the Finnish population. The impact of this legacy has already proven important in studies of common diseases, requiring active participation of even larger groups of the population.

5.5. Research funding

Table 5. Project funding during 1997-present

Project name	**Funding agency* (PI)****	**Funding k€**	**Years**
Finnish disease heritage	SA (LP) SA (OK)	390 35	1997-2000 1997-1999
Molecular biology of Finnish diseases	FO (LP, AJ, IU)	630	1997-2002
Molecular and cellular biology of aspartylglucosaminuria and NCL	SA (AJ)	376	1999-2007
Center of Excellence, Academy of Finland	SA (LP= coordin; AJ=PI)	423 197	2000-2005 2006-2008
Disease mechanisms in three NCL disorders	FO (AJ) GS (AJ students) FO (AJ students) FO (OK)	552 190 143 30	1997-2009 2001-2007 2002-2007 2003-2005
NCL-models	EU STREP (AJ=coordinator, LP=PI)	585	2004-2006
Systematic analysis of gene function	NCoE (AJ)	30	2007
Molecular biology of autoimmune diseases	SA (IU,LP)	84	2000-2001
Molecular pathology of APECED	SA (IU)	117	2000-2003
Molecular biology and genetics of APECED	FO (IU)	264	2000-2006
Function of the APECED protein	SA (IU)	94	2001-2002
APECED	SA (HK)	76	2001-2007
Immunological tolerance	SA (IU)	120	2004-2006
EURAPS, Autoimmune Polyendocrine Syndrome Type I -	EU (LP)	276	2006-2008

- A Rare Disorder of Childhood as a Model for Autoimmunity			
Molecular genetics and biology of lethal fetal syndromes	SA (MK) FO (MK) GS (MK students)	720 230 57	2003-2009 2003-2010 2005-2008
Molecular genetics of RAPADILINO syndrome	GS, FO (MK)	103	2004-2007
Genetic and environmental determinants of craniofacial syndromes	NIH (LP)	321	2005-2007

*EU=European Union, SA=Academy of Finland, TEKES=Finnish Funding Agency for Technology and Innovation, FO=Foundations, GS=graduate schools. **PI=see senior scientific personnel in chapter 5.8

5.6. Scientific collaboration

Anu Jalanko

Neuronal ceroid lipofuscinoses: Acad. Prof. Leena Peltonen (KTL), Prof. Anna-Elina Lehesjoki (Folkhälsän, Helsinki, Finland), Dr. Jonathan Cooper, (King's College, London, UK), Dr. Matti Jauhiainen (KTL), Dr. Hannah Mitchison, (University College, London, UK), Prof. Elina Ikonen (University of Helsinki, Finland), Dr. Jaana Tyynelä (University of Helsinki, Finland), Dr. Juha Saharinen (KTL), Dr. Massimiliano Gentile (University of Helsinki, Finland), Dr. Leonard Khiroug (University of Helsinki, Finland), Dr. Nisse Kalkkinen (University of Helsinki, Finland), Acad. Prof. Jussi Taipale (KTL), Dr. Liisa Myllykangas (Folkhälsän, Helsinki, Finland)

Ismo Ulmanen

APECED: Acad. Prof. Leena Peltonen (KTL), Prof. Ilkka Julkunen (KTL), Prof. Outi Vaarala (KTL), Dr. Juha Saharinen (KTL), Adj. Prof. Petteri Arstila (Haartman Institute, University of Helsinki, Finland), Prof. Jaakko Perheentupa (Helsinki University Hospital for Children and Adolescents, Finland), Prof. Jorma Palvimo (University of Kuopio, Finland), Prof. Olle Kämpe (Uppsala University, Sweden), Prof. Jacob Seeler (Institut Pasteur, Paris, France), Prof. Robyn Slattery (Monash University, Melbourne, Australia)

Leena Peltonen

PLOSL: Professor Panu Hakola (University of Kuopio, Finland), Dr. Lewis Lanier (University of San Fransisco, USA), Professor Ilkka Julkunen (KTL)

Marjo Kestilä

Lethal fetal syndromes: Acad. Prof. Leena Peltonen (KTL), Dr. Liisa Myllykangas (Folkhälsän, Helsinki. Finland), Adj. Prof. Riitta Herva (University Hospital of Oulu, Finland), Adj. Prof. Riitta Salonen (Family Federation, Helsinki, Finland), Adj. Prof. Anders Paetau (University Hospital of Helsinki, Finland), Dr. Kirmo Wartiovaara (University of Helsinki, Finland), Dr. Satu Kuure (University of Helsinki, Finland), Dr. Juha Saharinen (KTL), Prof. Brendan Lee (Baylor College of Medicine, Houston, Texas, USA)

5.7. Proposal for the future work and expected (societal) benefits (next five years)

Since the disease-causing genes and mutations behind diseases of the Finnish Disease Heritage have now been identified, the future studies will be focused on some special research problems facilitated by the resources we have built: Numerous mouse models will facilitate global analyses of target tissues and identification of involved molecular pathways behind critical disease processes e.g. neuronal degereration or aberrations of autoimmunity. Similarly, the produced cellular and *Drosophila* models will be used to identify pathways critical for normal development. Thus the ongoing investigations on the functional roles of the FDH gene products aim at the clarification of the molecular

pathology and novel therapeutic approaches for the respective diseases. Furthermore, this activity will be important for the maintenance and development of the skills and methods directly applicable for the functional studies of appearing genes behind the complex, polygenic diseases, which are intensively studied in MLO. In addition, we will develop the DNA-based diagnostic test panels for efficient carrier screening programs of FDH in the close collaboration with the clinical laboratory of the University Helsinki Central Hospital.

5.8. Senior scientific personnel

Leena Peltonen, M.D, Ph.D, Academy Professor 1987-
Anu Jalanko, Ph.D., adjunct professor, group leader 1993-
Ismo Ulmanen, Ph.D., adjunct professor, group leader 1998-
Marjo Kestilä, Ph.D., adjunct professor, Academy research fellow, group leader 2002-
Outi Kopra, Ph.D, adjunct professor, senior investigator 1996-1998, 1999-2006
Irma Järvelä, M.D., Ph.D., adjunct professor, senior investigator 1997-1998
Maarit Lehtovirta, Ph.D., post-doctoral fellow 1998-2000
Meelis Kolmer, Ph.D., post-doctoral fellow 1998-2001
Teppo Varilo, M.D, Ph.D, adjunct professor, senior investigator 1999-
Petra Eskelin, M.D, Ph.D., post-doctoral fellow 2000-2003
Minna Peltola-Laine, M.D., Ph.D., post-doctoral fellow 2000-2003
Hannele Kangas, Ph.D., post-doctoral fellow 2001-2003, 2006-2007
Aija Kyttälä, Ph.D, adjunct professor, senior investigator 2003-

5.9. 15 key references

Article	IF	No of citat.*
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* based on Web of Science August 2007

6 GENETIC EPIDEMIOLOGY

6.1. Research area and its significance

The impressive development of genome projects has resulted in the availability of total genome sequence information for over 350 organisms, including over 50 mammals on the Web (www.ncbi.nlm.nih.gov). This progress and the generated genome resources and technologies have dramatically increased our possibilities to define the biology of any human disease, including those with polygenic complex background and provide the possibility to obtain a genome-wide view to common diseases and their trait components. Eventually this information will lead to improved understanding of genetic versus life style risk factors and, at least in well developed health care systems, improve our possibilities to treat and prevent human diseases. However, many research challenges remain before excessive genome information can be translated to better health care of our societies. Several approaches will be needed to discover and characterize every disease-susceptibility gene and there is a growing realization that the primary resource needed to address most of the above-mentioned issues are well defined collections of samples from human populations that include extensive clinical information (F. Collins, Nature, Vol. 429, July 27, 2004 p. 475).

The goal of the research program is to capitalize the possibilities provided by the special population and well characterized study sample resources of Finland using updated molecular methods and new biocomputational strategies to collect genetic and molecular information of diseases with complex etiology. We aim to identify relationships between disease related phenotypes and genetic make up of individuals. We recognize that investigation of these relationships is hindered by 1) the imprecise definition and measurement of disease phenotypes 2) the heterogeneous genetic background, and 3) our limited knowledge about the mechanisms by which variations in DNA sequence can generate phenotypic effects and how these changes are related to other, life style risk factors or to the response of treatment. Overcoming these factors requires a highly integrated application of genetic, genomic, and biocomputational approaches in studies of the best possible study samples collected.

The Research Program on Genetic Epidemiology bridges the epidemiological, clinical and basic research, being well-rooted in the excellent clinical expertise and in the health care system of the special population of Finland and the great environment of Biomedicum Helsinki. Majority of our investigators also belong the prestigious, internationally evaluated National and Nordic centers of Excellence (www.aka.fi and www.ncoedg.org) as well as to the research program of Molecular Medicine of the Faculty of Medicine (research.med.helsinki.fi/molmed/), all multi-institutional organizations joining research group of KTL (both Department of Mental Health and Alcohol Research and with groups of the Department of Health and Functional Capacity), University, University hospital and Folkhälsan Research Center. These investigators occupy the 3rd floor of Biomedicum, making it really “the floor of molecular medicine” at Meilahti campus. The overall theme is to use excellent, clinically and epidemiologically well defined study samples to characterize the molecular background of diseases. The target diseases represent common diseases with complex genetic and life style risk factors: cardiovascular, neuropsychiatric and immunological diseases. After initial characterization of the involved genes and alleles we are in an excellent position to define genetic and environmental/ life style risk

factors for specific subtypes of the diseases and their trait components as well as to study the differences in drug response in patients with different genetic profiles. The molecular and biocomputational analyses needed in these efforts are greatly advanced by the expert infrastructure of the Biomedicum core facilities and the Finnish Genome Center in Biomedicum. The program takes a certain pride in significant support to their operations for all the investigators in Biomedicum, especially in biobanking, sequencing, biochip analyses, high throughput genotyping, bioinformatics and statistics and high throughput screening.

This research program aims to produce novel understanding of the genetic and life style risk factors predisposing to common human diseases representing major public health problems. We build on the integrated strengths of Finnish molecular genetics, epidemiology, computer sciences and biostatistics. Using the special population structure of Finland and the large population cohorts at KTL we aim to create new understanding of the role of genetic profiles in human disease processes and to establish new intellectual paradigms to be tested in global populations in our numerous international networks and collaborations. In this era of genome-wide technologies and biobanks Finland offers unique potential for becoming one of the leading countries in biomedical research. Our well established population history, unique families and epidemiological study samples with vast amount of clinical and life style information facilitate detailed studies of the etiology and molecular pathogenesis of human diseases.

The major goal of our current research is to identify predisposing genes and their risk alleles for major cardiovascular and neuropsychiatric diseases. We aim to capitalize the possibilities of the special population and epidemiological study sample resources of Finland in genome-wide analyses using molecular methods, across species comparisons and biocomputational strategies. Our special niche in the current era of genetics is based on the well defined Finnish study samples: Large pedigrees ascertained for specific diseases by our clinical collaborators and our access to the population cohorts, representing the whole population, collected during past 20 years from various geographical regions of Finland (Table 1.). The research will accelerate the discoveries of genetic profiles and gene-environment interactions leading to common human diseases. The research will pave the way to better understanding of complex diseases and their component traits, including the response to medications.

Table 1. Summary of our study samples, their genealogical origin and the clinical collaborators responsible for the study sample collection and characterization

Phenotype	**Geography, populations**	**Clinical collaborators**	**Study samples**
FCHL, Low HDL	Finland nationwide, Late settlement Eastern Finland, Dutch and UK study samples, MORGAM cohorts (Europe)	Marja-Riitta Taskinen, Markku Laakso, Leif Groop, Markku Savolainen, Alun Evans, Veikko Salomaa, T.W.A de Bruin	Large pedigrees, large populations cohorts
Myocardial infarct	Finland nationwide, Late settlement Eastern Finland, Canadian Quebec population	Markku Laakso, Marja-Riitta Taskinen, Veikko Salomaa, Kari Kuulasmaa, Jorma Viikari, Claude Laberge	Sib pair families, large population cohorts with identified cases
Schizophrenia	Finland nationwide; Late settlement Eastern Finland	Jouko Lönnqvist, Matti Isohanni, Timo Partonen	Nationwide collection of families, birth cohorts of 1966,1986
Autism and Asperger	Finland nationwide, Central Finland, US (AGRE) family collections	Lennart von Wendt, Taina Nieminen-von Wendt, Raija Vanhala, Irma Järvelä	Nationwide collection of families, births cohorts of 1966,1986
MS	Finland, high risk Vaasa county, Canadian Quebec population, UK population	Pentti Tienari, M-L. Sumelahti, George Ebers	Nationwide collection of large pedigrees and trios
Obesity	Finland, Late settlement Eastern Finland, Western Finland	Kimmo Kontula, Veikko Salomaa, Marja-Riitta Taskinen	Sibpairs, population cohorts

Detailed analyses of our unique study samples in an efficient way requires the most updated high-throughput genotyping, sequencing and transcript profiling methodology. Further, system-biology based approaches relying on high-throughput biological experiments and computational analyses facilitate identification of critical pathways involved in the disease processes. The integrated expertise of the investigators of the Program and it's collaborators both nationally and internationally provides a highly competitive setting for studies of molecular etiology of complex diseases. It should be emphasized that integrated analyses of complex data sets collected from human (and model orgnisms) requires construction and harmonization of databases and development of novel biocomputational and biostatistical strategies. During past 10 years MLO has made a special effort to recruite experts in databases and statistical analyses. We have become one of the leaders in databases related to biobanking in Europe and substantial amount of our external competitive research funding is used to these infrastructures (www.biobanks.eu). The graph below indicates the platforms and competences we have established for large study samples and data sets as well as the critical national and international links and collaborations related to these activities.

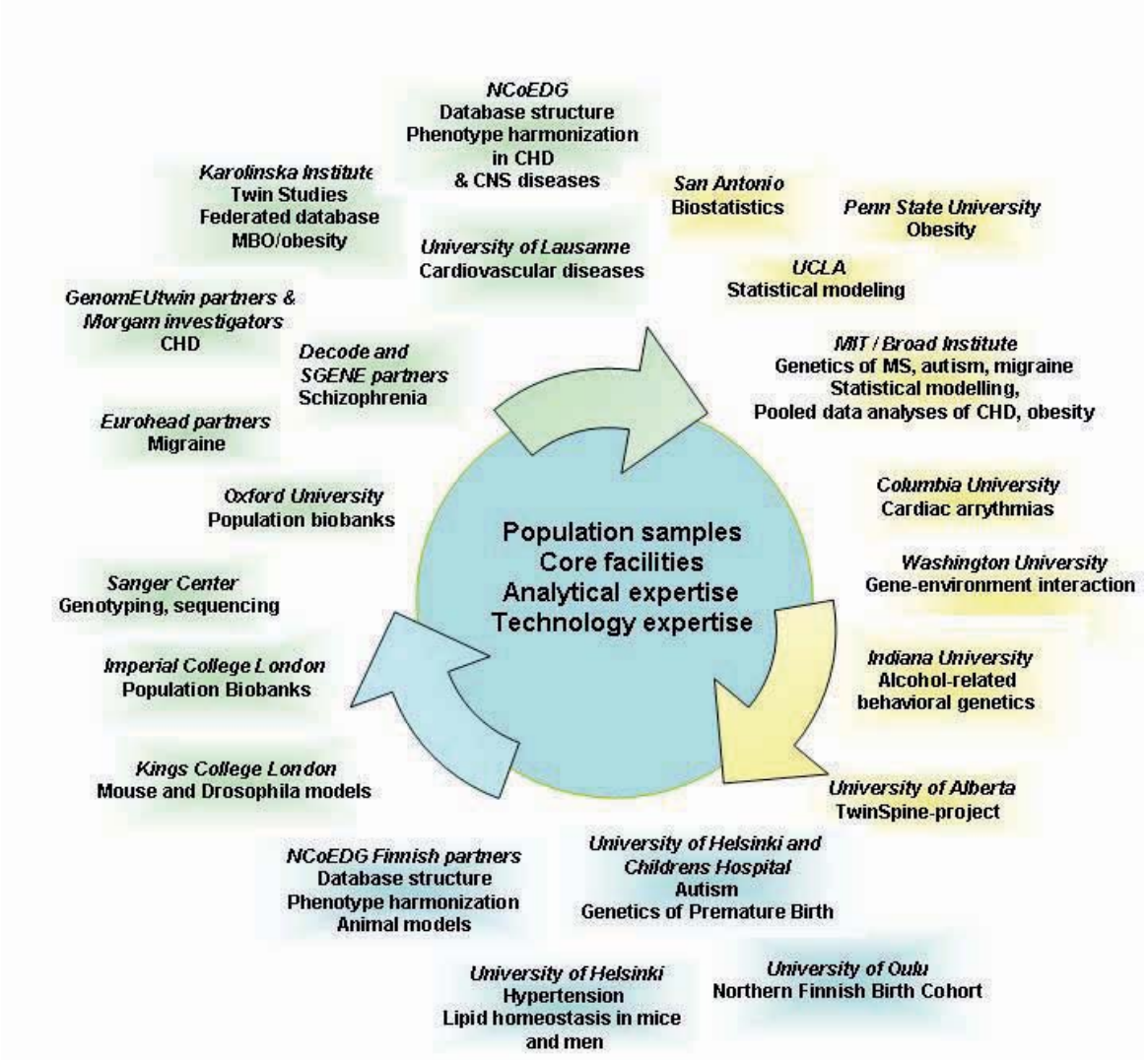

Figure 1. The graph indicates the platforms and competences established for large study samples and data sets as well as the critical collaborations related to these activities.

6.2. The main achievements

Our research efforts during past 10 years in complex diseases has resulted in the mapping of total of 18 loci for complex traits with the genome-wide level of significance, the majority of these findings being replicated in other study samples from more heterogeneous populations. Further, we have established solid evidence of an associated allelic variant for seven complex disease genes in Finnish study samples and by our international collaborations in most cases replicated the findings in non-Finnish populations. Functional analyses have so far been focused on the specific allelic forms identified or on monogenic diseases providing information of pathways relevant for common diseases. Special interest has been paid on the special complications or severe trait components of target traits. Specifically, the following accomplishments have been obtained during past ten years.

- Tentative 18 disease or trait component loci have been mapped and further restricted using linkage disequilibrium and haplotype sharing strategy and dense SNP mapping. New statistical analyses have been developed to maximize the use of information of the population structure.
- Susceptibility loci have been mapped and at least some putative genes and their allelic variants identified for lactose intolerance, familial combined hyperlipidemia, MS, familial obesity, familial schizophrenia, autism and adult height. Additional susceptibility loci have been identified also in migraine, hypertension, height, BMI, nicotine addiction and preference for sweet.
- The relationship between the mutation background and environmental/life style risk factors or treatment response has been analyzed in the collaborative effort with Finrisk investigators and within our GenomEUtwin project of European twins. This has resulted in the initial identification of some joint effects behind cardiovascular disease events.
- Our in vitro (cellular) and/or in vivo (mouse) models for both numerous monogenic diseases, like APECED (autoimmune model), PLOSL, (demyelination and neuropsychiatric disease model), as well as for specific alleles of the USF1 gene (a risk gene behind dyslipidemias) and mouse crosses for anxiety are being used to study functional consequences of mutations in target tissues and have exposed putative defective pathways relevant for common diseases.

Identification of complex disease genes

Our major strategy for final gene identification has relied on the concept of shared haplotypes among affected individuals in exceptional families or regional collection of patients. This is well exemplified by our reports on the associated genes in families with lactose intolerance, dyslipidemias, obesity, familial combined hyperlipidemia, schizophrenia. For all these traits, the involved gene was initially identified in exceptional families by positional cloning. For autism, multiple sclerosis and schizophrenia, an exceptional regional enrichment of cases or families exists in mid-Finland (autism), in Vaasa region (MS), representing an early settlement region with high level of inbreeding, and in Kuusamo, an internal subisolate on the eastern boarder of Finland, inhabited in 1750's (schizophrenia). These efforts have provided evidence except for the involved gene, but also identified allelic forms defined by common SNP variants, typically in non-coding or regulatory regions of these genes. The identified genes are remarkably interesting: a transcription factor USF1 for dyslipidemias, a protein kinase for MS and a novel gene, critical for neuronal development in Asperger syndrome and schizophrenia (DISC1).

Many of our research efforts have been fundamental for international collaborations. Dr. Peltonen has co-ordinated an international collaboration within MS, which has replicated the PRKCA1 findings in Canadian, Swedish and Danish populations. Recent collaborative effort coordinated by Dr. William Hennah, currently in Edinburgh, tested the significance of DISC alleles in global study samples of schizophrenia and the EU funded GenomEUtwin (also coordinated by Dr. Peltonen) study has combined data from over 300 000 twin pairs (www.genomeutwin.org). Dr. Peltonen is also the head of the governance board of the recently funded ESFRI (European Strategic Forum for Research Infrastructures) effort for Biobanking and Biomolecular Resources (BBMRI).

Finally our tight collaborations with UCLA and the Broad Institute have facilitated a number of international projects funded by NIH (Dr. Peltonen as the P.I.) typically using Finnish population samples in GWA studies or deep sequencing efforts to characterize the genetic profiles behind cardiovascular or neuropsychiatric diseases).

Some of the gene variants identified by us seem to be associated also with subtraits or quantitative features of these diseases. The risk allele of USF1 is correlated with high triglyceride levels in man and provides an increased risk for early cardiovascular events in women. DISC1 risk allele shows an association both with psychosis generally as well as with the QTL of specific neurobehavioural trait components, known to be associated with an increased risk of schizophrenia.

Genetic loci identified for complex diseases in the Finnish study samples

Following genome scans we have well defined loci for total of 12 diseases. Restriction of the critical, disease-associated regions for all these traits has been systematically carried out using linkage disequilibrium (LD) and allele sharing in disease alleles, relying on the dense set of single nucleotide polymorphisms and information of LD and haploblock intervals in Finns.

Table 2. Summary of identified common disease loci and genes identified by us

Phenotype	**Chromosome**	**Gene**	**Reference**
Three novel MS-loci	18q,5p,17q	Myelin basic protein, C7, PRKCA	Tienari et al. 1994 , Kuokkanen et al. 1996, 1997, Saarela et al. 2002, 2006, Kallio et al. manuscript
One major FCHL-locus, two "modifying" loci	1q, 10q, 2q	USF1 (1q)	Pajukanta et al. 1998, 1999, 2004
Three loci for low HDL	8q, 16q, 20q	n.d.	Soro et al. 2002, Pajukanta et al. 2003
One hypertension locus	3q	AT	Kainulainen et al. 1999, Perola et al. 2000
One locus for osteoarthritis	2q	n.d.	Leppavuori et al. 1999
Three loci for schizophrenia	1q,7q, 5q	DISC1, Reelin, n.d.	Hovatta et al. 1999, Ekelund et al. 2000, Paunio et al. 2001, Hennah et al. 2003, 2006, Peltonen et al. 2006
Two loci for coronary heart disease	2q,X	n.d.	Pajukanta et al. 2002
Thee loci for migraine	4q, 17p, 18q	n.d.	Wessman et al. 2002, Anttila et al. 2006
Multiple loci for stature	1q,7q,8q,X	Col12A1	Perola et al. 2001, Sammalisto et al. 2006, Perola et al. 2007
Two loci for obesity	18q,X	n.d, SLC6A14	Ohman et al. 2000, Suviolahti et al. 2003
Three loci for autism and Asperger syndrome	3q, 1q, 15q	n.d., DISC1	Auranen et al. 2002, Rehnstrom et al. 2006, Ylisaukko-oja et al. 2005, 2006

Three loci for bipolar disease	Xq, 4q, 16p 16p	n.d.	Pekkarinen et al. 1995, Ekholm et al. 2003
Locus for sweet preference	7q,10q,11p	FTO	Keskitalo et al. manuscript
Three loci for nicotine addiction		n.d.	Loukola et al. 2007

Functional studies of identified disease alleles and characterization of their role in disease

Although the major focus of our research effort so far has been in the identification of genes and genetic profiles behind common diseases, we here provide some examples of functional studies performed by us. For the USF1 behind dyslipidemias and early myocardial infarct, we have demonstrated that the risk allele shows allelic imbalance and abnormal reactivity to insulin both in fat and muscle as well as abnormal transcript profiles of the downstream genes for the USF1 in fat and muscle biopsies of individuals carrying the risk alleles. Further, to demonstrate the role of a specific allele at the level of the vessel wall of myocardial arteries we have shown in the Helsinki Sudden Death Study sample of 700 males that risk allele carriers show wide plaques and more advanced atherosclerosis. We have also produced a knockout mouse model for USF1 to address in detail the tissue specific functions of this dyslipidemia gene. For migraine, genome wide expression studies of rodent models with mutations in genes causing Mendelian forms of migraine have been used to identify common pathways and subsequently positional candidate genes for common forms of migraine. Even for behavioural traits rodent models have been useful: Mouse crosses have facilitated the unbiased search for aberrations in global transcript profiles and when combined with behavioral anxiety-measures, exposed 17 genes that regulate anxiety-like behavior by Dr. Hovatta. These results have been validated by local lentivirus-mediated gene transfer (overexpression and silencing by RNAi) experiments that have shown that glyoxalase 1 (Glo1) and glutathione reductase 1 (Gsr), regulate anxiety-related behavior in mouse *in vivo.* Allelic diversity of these genes is now being analyzed as part of the Finnish population-based Health 2000 study. A representative sample (n=6005) of Finland's adult population was interviewed with CIDI (Composite International Diagnostic Interview) for the presence of anxiety disorders. The anxiety disorder sub-cohort consists of 339 cases and 678 matched controls.

Multiple studies have been performed to address the role and the population impact of identified variants for the disease or trait components of the disease in large nationwide family collections or population cohorts of KTL (Table 3.).

Table 3. Sample collections of the population cohorts

Cohort	Total cohort (n)	DNA samples (n)(%)	Average DNA yield**	Serum (n)	Other samples***
ATBC study	29 000	2122 (7.3)*	144	29 000	n
Finnish Twin Cohort	42 000	12040 (28.7)	324	1 000	sess
Finrisk 1992-2007	29 597	27150 (89.5%)	278	From all	sess
92	6051	5784	154	6025	sess
97	8447	8791	285	7150	sess
02	8799	8758	300	8788	sess
07	6300	6300	300	6300	sess
Helsinki Sudden Death Study	1400	1400 (100)	-	700	ft, pt(ss), u(ss)
Health 2000	7419 (8000)	6824 (91.9)	401	8000	sess
KTL Psychiatric collections	9728	2142 (22.0)	240	-	c(ss)
Northern Finland Birth Cohort 1966 & 1985-86	~12 000	11652	300	From all	p, sess
Helsinki Sudden Death Study	~1 000 000	0	0	0	pt, c(ss), ft(ss)
Mobile Clinic Health Survey	57 000	0	0	57 000	p
Mini-Finland	7217	0	0	7217	p, u

Total 212 358 biological samples. ss=subsample; sess =several subsamples; *extraction unfinished, samples from all; **amount still left; ***plasma= p; frozen tissue = ft; tissue in paraffin =pt; urine= u; cells= c; nail clippings =n

A good example of these efforts are the risk effects of 2.2-3.2 identified for the combination of risk alleles of USF1 and ApoA5 for cardiovascular risks in Finrisk 92 and 97 with over 120 000 follow-up years total, as well as additive effect of combination of risk alleles for serum levels of cholesterol, TG, LDL and HDL observed in genotyping the risk variants of the full Finrisk 97 cohort (over 6000 individuals). To develop better tools to address the impact of risk alleles for disease outcomes we have collaborated with top level epidemiologists and mathematicians and adapted e.g. the decision tree models to identify how study how the risk alleles modify the disease risk in population groups with traditional risk alleles. In these efforts we are greatly helped by our collaborations with The Finnish Distinguished Professor of the Academy of Finland, Joel Terwilliger as well as the group of the Academy Professor Heikki Mannila in the Helsinki Institute of Information Technology.

Table 4. Association of pair-wise SNP combinations with the endpoints in time-to-event analysis (covariates: age at baseline, (sex, cohort), smoking, hypertension, rchol, BMI, diabetes, CRP). The allele stated as the risk allele was coded as 1 and the other allele as 0.

SNP	Gene	Inheritance Model	Group	FINRISK-92 HR (CI 95%) p	FINRISK-97 HR (CI 95%) p	Combined HR (CI 95%) p	FDR [c]
*Rs7542281*x *Rs1042580*	*F5* *THBD*	Recessive [a] Dominant [a]	CHD, women	4.51 (1.40-14.54) 0.012	7.14 (2.09-24.36) 0.0017	4.45 (1.94-10.19) 0.00042	+
*Rs5030341*x *Rs1401296*	*ICAM1* *PROC*	Dominant [a] Dominant [a]	Death, men	2.53 (1.03-6.20) 0.043	2.68 (1.50-4.76) 0.00081	1.63 (1.18-2.24) 0.0028	+
*Rs2269648*x *Rs1401296*	*F5* *PROC*	Dominant [b] Dominant [a]	Death, men	1.20 (0.86-1.66) 0.28	1.07 (0.80-1.44) 0.65	1.80 (1.18-2.76) 0.0069	+
*Rs5030347*x *Rs1401296*	*ICAM1* *PROC*	Recessive [a] Dominant [a]	CHD, women	4.29 (0.38-47.97) 0.24	1.50 (0.22-10.08) 0.68	2.08 (1.21-3.57) 0.0083	-
*Rs7542281*x *Rs1401296*	*F5* *PROC*	Recessive [a] Dominant [a]	CVD, all	1.51 (0.94-2.44) 0.091	1.50 (1.02-2.21) 0.037	1.49 (1.11-2.01) 0.009	-
*Rs6025*x *Rs6048519*	*F5* *THBD*	Dominant [a] Dominant [a]	CVD, men	1.53 (0.76-3.08) 0.23	5.09 (1.39-18.68) 0.014	2.80 (1.42-5.53) 0.0029	-
*Rs7542281*x *Rs1401296*	*F5* *PROC*	Recessive [a] Dominant [a]	Stroke, all	3.00 (1.23-7.31) 0.016	2.00 (0.93-4.32) 0.077	2.69 (1.35-5.35) 0.0050	-
*Rs1401296*x *Rs6048519*	*PROC* *THBD*	Recessive [a] Dominant [a]	Stroke, men	1.38 (0.33-5.76) 0.66	3.13 (1.06-9.27) 0.039	3.42 (1.30-8.99) 0.013	-

[a]Minor allele is the risk allele, [b]Major allele is the risk allele, [c]FDR: Rejecting the null-hypothesis for those with "+" assures that the false discovery rate <10% in the combined analysis.

Systems Biology

System biology was initiated with the recruitment of Dr. Jussi Taipale into KTL at 2005. His group has used cell cycle pathways as a proof of principle of the system biology approach to tackle molecular pathways in complex biological processes. The main achievements of the systems biology group, on board only in 2005-2007 are 1) identification of genes regulating cell size and cycle progression in *Drosophila* and in humans, 2) development of tools allowing prediction of regulation of genes based on sequence (including prediction of the effect of SNPs on gene expression), and 3) characterization of genes involved in mammalian Hedgehog signal transduction (a signalling pathway activated in several forms of human cancer).

In genome-wide analyses of protein phosphorylation in regulation of the cell cycle in Drosophila S2 cells, and screened 14 000 dsRNAs in the Drosophila Gene Release I and II dsRNA libraries in multivariate flow cytometry assay in triplicate. This analysis resulted in the identification of a number of genes and pathways that have not previously been linked to regulation of the cell cycle.

For analyzing organ specific growth control, a high-throughput assay was developed for analysis of transcription factor binding specificities, and this method was used to

measure the DNA binding profiles of GLIs 1-3, Tcf4 and c-ETS1, which mediate transcriptional responses to the Hedgehog, and Wnt and Ras/mitogen-activated protein kinase signaling pathways, respectively. To identify enhancer elements regulated by these pathways a novel computational tool EEL has been developed in collaboration with Dr. Kimmo Palin and Esko Ukkonen (University of Helsinki, Department of Computer Science) to align DNA sequence based on TF binding sites in all identified human and mouse genes. The resulting data was used to identify Hh and Wnt target genes, and to predict TFs that are activated in an experiment on the basis of changes in expression of a limited number of genes. Identification of tissue-specific enhancer elements has substantial potential significance for our understanding of complex disease genetics.

6.3. Scientific impact

Table 5. Summary of the scientific output during 1997-2007

Scientific output	**N**	**Comments**
Peer-review articles in international journals	257	In addition 27 review articles/book chapters. See Appendix 2
Invited lectures and chairmanships in international meetings	>600	Examples of plenary and keynote lectures : - Leena Peltonen: "Story of My Roots: Disease Mutations of a Population". Margaret Pittman Lecture, part of the NIH Director's Lecture series. Los Angeles, California, USA, January 28, 2004. - Leena Peltonen: "From families to populations: impact of disease genes" HGM 10th Human Genome Meeting, Kyoto, Japan, April 18-22, 2005. - Leena Peltonen: "Genome-wide view to human diseases and the special value of twin studies in the post-genome era". ISTS (The International Society for Twin Studies) Mid-Congress Conference, Los Angeles, June 29, 2005. - Leena Peltonen: "From families to population: Lessons from disease genes of a genetic isolate". ASHG Meeting, Salt Lake City, Utah, USA, October 25-29, 2005. - Leena Peltonen: "European strengths in biomedical research in postgenome era". From Biobanks to Biomarkers: Translating the potential of human population genetics research to improve the quality of health of the EU citizen, Hinxton, UK, September 20-23, 2005. - Leena Peltonen: "From Families to Population: Example of Finland". Keystone Symposia, Genome Sequence Variation and the Inherited Basis of Common Disease and Complex Traits, Big Sky Resort, Big Sky, Montana, January 8-13, 2006 - Leena Peltonen: "Human Disease Genes: From Families to Populations". 11th International Congress of Human Genetics, Brisbane, Australia, August 6-10, 2006. - Leena Peltonen: "Low hanging fruits and beyond, genetics of common traits". HGM 12th Human Genome Meeting, Montreal, Canada, May 19-25, 2007. - Leena Peltonen: "The GenomEUtwin project". ICTS Meeting, Twin and multiples – a life course perspective, Ghent, Belgium, June 8-9, 2007.

Invited lectures and chairmanships in international meetings		- Leena Peltonen: "Genome-wide strategies to address molecular pathways of atherosclerosis". European Atherosclerosis Society 76th Congress, Helsinki, Finland, June 10-13, 2007. - Leena Peltonen: "Beyond associations, understanding complex characters of common traits". The Genomics of Common Diseases Conference, Wellcome Trust Conference Center, Hinxton, UK, July 7-10, 2007.
Articles in domestic journals and text books	18	See Appendix 2
Lectures in domestic meetings and teaching lectures	>300	
Editorial tasks in international journals	14	e.g. Psychiatric Genetics 1989–; European Journal of Human Genetics 1991 – 2004; American Journal of Medical Genetics 1992–; Current Opinion in Genetics & Development 2000–
Committee memberships: domestic and gate keeper positions (domestic)	12	e.g. Chairman of the Medical Research Council of Finland (Academy of Finland) 1997; Science and Technology Policy Council of Finland, Member 1997–1998
Committee memberships: international (EU, WHO etc.)	16	e.g. EURESCO Scientific Steering Committee, Member 1997–1998; International Bioethics Committee, UNESCO, Member 1998–2003; American Society of Human Genetics, Member, Board of Directors 2001–2004; Chair, Populations and Public Health Strategy Committee, Wellcome Trust 2004-; HUGO – President 2005–
Membership of scientific organizations	5	e.g. European Molecular Biology Organization (EMBO), Elected Member 1991- ; European Academy of Sciences (Academiae Europeae), Elected Member 1999– ; Foreign Associate Member in the Institute of Medicine of the National Academies, USA 2006–
International evaluation panels (EU etc.)	12	e.g. Scientific Advisory Board, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden, Member 1996– ; Scientific Advisory Board of the Genome Research Programme, Foundation for Strategic Research, Sweden, Member 1999–2005; International Advisory Board, SWEGENE, Sweden, Member 2000–2004; Scientific Advisory Board of UK Biobanks, Member 2001– ; Scientific Advisory Board of the Shanghai Genome Center, Member 2002– ; Scientific Advisory Board, Genome Canada, Member 2002 – 2003
Organizing committee of international meetings	22	e.g. EMBO Practical Course – SNP genotyping and Haploblock Analysis, August 2005, Helsinki, Finland; HGM2006 – Human Genome Meeting, May, 2006, Helsinki, Finland; GenomEUtwin Scientific Meeting, European network of twin registers and MORGAM cohorts, December, 2006, Rome, Italy
Doctoral dissertations	20	See Appendix 2
Supervision of dissertations: ongoing	44	

Opponent of dissertations		National universities 6 Foreign universities 10
Pre-examiner of - dissertations - adjunct professors - professorships		 12 6 12
Prizes	11	e.g. EMBO Young Investigator 2006 (J.Taipale); European van Gysel Prize for Biomedical Research 2006 (L.Peltonen); Eric K. Fernströms Stora Nordiska Priset 2006 (L.Peltonen)

6.4. Societal impact

The final goal of genetic and genomic/system biology related research is to translate the wealth of data emerging from large-scale research efforts in genetic and genomic epidemiology conducted in well-characterized Finnish (and European) samples into information of relevance to future clinical and public health advances. The aspiration is to make use of large epidemiological datasets to help to define the precise aetiological DNA, RNA or protein variants, and to understand their joint effects (and interactions) with other variants and relevant life style exposures. We expect that the information gathered will be relevant to the practice of clinical medicine and public in two major respects: through advances in understanding of the pathogenesis of disease, and through the enhanced potential to use genetic and genomic information (including biomarkers) to stratify risk, monitor progression and predict therapeutic response to common health problems.

Implementation of this new research date needs to be sensitive to the ethical, legal and social implications of such developments. Finland is in many ways an ideal setting for close integration between the scientific and clinical research and examination of the broader "societal" consequences of such research. In the setting of national health care system with a tradition of excellent communication with public and high acceptance of medical research the fruits of genome research can be expected to produce tangible benefits for Finnish (and European) citizens. Already now, the most commonly used DNA test in Nordic countries is the one detecting lactose intolerance, developed based on our innovation. Similar successes for DNA testing providing more accurate diagnosis and providing guidance to improved medication and intervention strategies in numerous old age diseases can be expected. The strength of Finnish genome research is more societal than technical. We can use the large clinical study samples and population cohorts at our disposal to understand the population-level effects of all biological variants identified by us and others. In the case of T2D for example, we can estimate based on published findings, that in Europeans, it is currently possible to achieve a discrimination index for a diagnosis of T2D of ~63%. This still lies some way short of the ~75-80% benchmark considered appropriate for clinical utility, but the potential for further discoveries in T2D genetics means that this benchmark is far from unattainable. Finnish study samples make it possible to evaluate the impact of common and rare alleles and their cross talk with traditional life style risk factors, improve the use of existing therapeutics and develop clinical diagnostics for prediction, prognostication, screening and "personalized" therapeutics.

6.5. Research funding

Table 6. Project funding during 1997-present

Project name	**Funding agency* (PI)****	**Funding k€**	**Years**
Limiting the immune response in adenoviral gene therapy in the brain -application to Parkinson's disease	EU (TP)	100	1997-1998
Multiple Sclerosis	EU (LP)	309	1997-2000
Genetics of common diseases: integrated approach to genome-wide profiling of common traits	FO (LP)	600	1997-2006
Several Ph.D. projects	GS (LP students)	318	1997-2009
Monica Cohort	EU (LP)	78	1998-2001
Center of Excellence in Disease Genetics	SA (LP)	900	2000-2005
Molecular Genetic and neurocognitive profiles in autistic spectrum of disorders	SA (LP)	96	2000-2003
GenomEUtwin, Genome-Wide Analysis of European Twin and Population Cohorts to Identify Genes in Common Diseases	EU (LP)	3 336	2002-2007
Genetic Loci Predisposing to Multiple Sclerosis (MS)	FO (LP)	354	2002-2007
Characterization of genetic loci predisposing to multiple sclerosis	HUS EVO (LP)	252	2002-2004
Post Doctoral salary costs, genomewide analyses of background of common disease	SA (LP)	204	2003-2007
Research costs for acad. Prof., genomewide analyses of background of common disease	SA (LP)	780	2003-2008
Compgenome; New computational techniques for analysing the structural and functional landscape of the mammalian genomes	SA (LP)	183	2004-2007
Genetic analysis of schizophrenia phenotype clusters using advanced statistical approaches	CO (LP)	120	2004-2007
Characterization of the genetic background of Multiple Sclerosis	NIH (LP)	130	2004-2005
Preparing funding for EU-project	SA (LP)	50	2005,2007
Neuropromise, Neuroprotective Stragegies for Multiple Sclerosis	EU (LP)	471	2005-2009
GEHA, Genetics of Healthy Aging	EU (LP)	236	2005-2010
Genes and underlying metabolic pathways in MS	HUS EVO (LP)	310	2005-2009
Center of Excellence in Complex Disease Genetics	SA (LP)	450	2006-2008
Population Biobanks, Promoting Harmonising of Epidemiological Biobanks in Europe	EU (LP)	49	2006-2008

Utilizing whole-genome association strategy to locate genetic variants predisposing for cardiovascular disease	FO (LP)	180	2006-2008
Autism	FO (LP)	120	2006-2007
Molecular genetic study of schizophrenia and cognitive defects in Finnish family-based sample	HUS EVO (TP) FO (TP)	66 35	2002-2003 2005-2006
Molecular genetic study of mood disorders: depressive and bipolar disorders and the seasonal pattern in Finland	SA (TP)	120	2004-2006
Molecular genetic study of mood disorders in Finland	HUS EVO (TP) FO (TP)	45 20	2005-2006 2005
Disorders of sleep regulation: basic mechanisms and therapeutic perspectives	EU (TP)	120	2005-2008
Genetic architecture of sleep and the role of sleep/sleep loss in development of mood disorders	HUS EVO (TP)	90	2006-2008
Utilizing whole-genome association strategy to locate genetic variants predisposing for cardiovascular disease.	FO (MP)	40 150	2002-2004 2005-2008
Capturing and verifying the role of the genetic variation of functional and positional candidate loci in relation to cardiovascular disease in a Finnish population sample	FO (MP)	40 30	2003-2005 2007-2008
Food preferences and chemosensory performance: genetic parameters addressed in twin and population cohorts	SA (MP)	273	2004-2007
Power tools for linkage and LD analysis for complex etiological models	SA (MP)	100	2005-2007
Growth control and Cancer	FO (JT)	390	2005-2007
Net2Drug	EU (JT)	82	2007
Genetics and neurobiology of anxiety	SA (IH) FO (IH)	182 107	2006-2009
The effect of gene copy number variation on insulin resistance and related quantitative traits	Novo Nordisk Fonden (KS)	20	2006-2008

*EU=European Union, SA=Academy of Finland, TEKES=Finnish Funding Agency for Technology and Innovation, FO=Foundations, HUS EVO=University Central Hospital.
**PI=see senior scientific personnel in chapter 6.8

6.6. Scientific collaboration

Leena Peltonen

Complex Disease Genetics: Prof. Mark Daly, Prof. David Altschuler (The Broad Institute, Cambridge, USA), Prof. Mark McCarthy (Oxford University, UK), Prof. Marja-Riitta Taskinen (University of Helsinki, Finland), Prof. Leif Groop (Lund University, Sweden), Prof. Jouko Lönnqvist (KTL), Professor David Porteous (Edinburgh University, UK)

GenomEUtwin: Prof. Nick Martin (Queensland Institute of Medical Research, Brisbane, Australia), Prof. Tim Spector (King's College London, UK), Prof. Dorret Boomsma (Netherlands Twin Register, Amsterdam, Netherlands), Prof. Nancy Pedersen (Swedish Twin Registry, Stockholm, Sweden), Prof. Jaakko Karprio (University of Helsinki, Finland)

Population cohorts: Prof. Veikko Salomaa, Prof. Kari Kuulasmaa (KTL), Prof. Marjo-Riitta Järvelin (Imperial College, London, UK), Dr. Kari Stefansson (deCODE, Reykjavik, Iceland)

Mathematic Modelling: Prof. Heikki Mannila (Helsinki Institute for Information Technology, Finland), Prof. Joe Terwilliger (University of Helsinki, Finland and Columbia University, New York, USA), Prof. Peter Donnelly (Oxford University, UK), Prof. Mark Daly (The Broad Institute, Cambridge, USA)

Jussi Taipale

Systems biology: Prof. Timothy Hughes (University of Toronto, Canada), Prof. Joerg Hoheisel (German Cancer Research Center, Heidelberg, Germany), Prof. Olli Kallioniemi (Technical Research Centre**,** Turku, Finland), Prof. Juha M. Partanen (University of Helsinki, Finland), Prof. Lauri A. Aaltonen (University of Helsinki, Finland)

Markus Perola

Quantitative genetics: Prof. Pekka Karhunen (University of Tampere, Finland), Prof. Joseph Terwilliger (University of Helsinki, Finland and Columbia University, New York, USA), Prof. Hely Tuorila (University of Helsinki, Finland), Prof. Alun Evans (University of Belfast, UK), Prof. Claudio Francesci (University of Bologna, Italy), Dr. Harald Göring (Southwest Foundation of Biomedical Research, San Antonio, US)

Tiina Paunio

Disorders of mood and sleep: Prof. Erkki Isometsä (University of Helsinki, Finland), Adj. Prof. Timo Partonen, Adj. Prof. Annamari Tuulio-Henriksson (KTL), Adj. Prof. Tarja Stenberg (University of Helsinki, Finland), Prof. Jaakko Kaprio (University of Helsinki, Finland), Prof. Markku Koskenvuo (University of Helsinki, Finland), Prof. Reto Huber (University of Zurich, Switzerland), Prof. Tom de Boer (Leiden University Medical Center, The Netherlands), Prof. Nelson Freimer (University of California, Los Angeles, USA)

Iiris Hovatta

Molecular genetics and neurobiology of anxiety disorders: Acad. Prof. Leena Peltonen, Prof. Jouko Lönnqvist, Dr. Sami Pirkola (KTL), Prof. Joseph D. Terwilliger (University of Helsinki, Finland and Columbia University, New York, USA), Dr. Matthew Zapala, Prof. Nicholas Schork and Prof. Victoria Risbrough (UCSD, San Diego, USA), Dr. Dario Greco (University of Helsinki, Finland), Prof. Esa Korpi (University of Helsinki, Finland), Dr. Jin-Hui Wang (Chinese Academy of Sciences, Beijing, China), Prof. Juha Kere (University of Helsinki, Finland), Adj. Prof. Sami Pirkola, Adj. Prof. Jaana Suvisaari (KTL)

6.7. Proposal for the future work and expected (societal) benefits (next five years)

With the rapidly emerging data from genome wide association studies in large case-control study samples, new potentially associated genes will be identified. However, these "low hanging fruits", typically representing common SNPs and showing the increased risk at the 1.05-1.2 level will not explain the complete genetic background of common diseases. The prestigious Finnish study samples and population resources available at KTL will be critical in the next phase of these studies: We need to fine-map the aetiological variants, identify full allelic spectrum behind the disease (both common and rare alleles) and to explore issues of pleiotropy and heterogeneity. Population-based cohorts will be central to efforts to understand the epidemiological characteristics of the variants we and others will identify in genome-wide association studies and to explore the scope of joint effects between risk alleles/haplotypes and between genes and environmental and lifestyle factors

Based on our systematically built expertise, core facilities and collected study samples we are convinced that MLO, as a critical part of FIMM, will make a substantial and unique contribution to the identification and characterization of specific functional

variants and genetic profiles behind complex diseases and their trait components as well as in estimation of their relationship with lifestyle risk factors.

We expect to be in a position where, at least for some of the variants, we can evaluate disease pathogenesis, explore population-based effects, evaluate the impact of common and rare alleles and their joint effects with traditional life style risk factors, improve the use of existing therapeutics and develop clinical diagnostics for prediction, prognostication, screening and 'personalized' therapeutics. If sufficient resources can be obtained, genetic epidemiological research at KTL would contribute significantly to the actions of our health care providers and public health officials and thus serve the betterment of the Finnish health care system and contribute to improved understanding of the background and causes of common diseases worldwide.

6.8. Senior scientific personnel

Leena Peltonen, M.D., Ph.D., Academy professor, group leader 1987-
Helena Kääriäinen, M.D., Ph.D., Research Professor 2007-
Jussi Taipale, Ph.D., professor (Academy professor 1.1.2008→), group leader 2005-
Markus Perola, M.D., Ph.D., adjunct professor, group leader 2002-
Tiina Paunio, M.D., Ph.D., adjunct professor, senior investigator 1998-
Teppo Varilo, M.D., Ph.D., adjunct professor, senior investigator 1999-
Janna Saarela, MD, Ph.D., senior investigator 2000-
Kaisa Silander, Ph.D., senior investigator 2002-
Anu Loukola, Ph.D., senior investigator 2003-
Iiris Hovatta, Ph.D., adjunct professor, senior investigator 2004-
Minna Taipale, Ph.D., senior investigator 2005-
Nabil Enattah, MD, Ph.D., post-doctoral fellow 2005-
Martin Boenke, Ph.D., post-doctoral fellow 2005-
Björklund Mikael, Ph.D., post-doctoral fellow 2005-
Li Song-Ping, Ph.D., post-doctoral fellow 2005-
Päivi Laiho, Ph.D., head of the laboratory 2006-
Teemu Kivioja, Ph.D., post-doctoral fellow 2006-
Wei Gonghong, Ph.D., post-doctoral fellow 2006-
Salim Mottagui-Tabar, senior investigator 2006-2007
Eveliina Jakkula, MD, Ph.D., post-doctoral fellow 2006-
Samuli Ripatti, Ph.D., senior investigator 2007-
Mikko Kuokkanen, Ph.D., post-doctoral fellow 2007-

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* based on Web of Science August 2007

7 MOLECULAR BIOLOGY OF CARDIOVASCULAR DISEASES

7.1. Research area and its significance

Atherosclerotic cardiovascular diseases are the major causes of death in western societies. The prevalence of coronary artery diseases (CAD), however, increases rapidly also in developing countries and formerly socialist economies of Europe. Thus, within the next 15 years, CAD are expected to be the main cause of death globally. Also in Finland, despite a considerable decrease in serum total cholesterol levels since the start of the North Karelia Project in the 1980's, a large part of the population still has an increased risk of CAD and atherosclerosis. This mainly is due to a rising incidence of type 2 diabetes, obesity, and metabolic syndrome. Although the serum high-density (HDL) cholesterol levels have increased among a part of the Finnish population, about 30 % of the population still has too high total as well as low-density lipoprotein (LDL) cholesterol concentrations. This data is based on the recent comprehensive health examination, the Health 2000 Health Examination Survey coordinated by National Public Health Institute.

HDL and atherosclerosis

An inverse correlation between the risk for developing premature CAD and the serum HDL cholesterol has been substantiated in a number of epidemiological and interventional studies. HDL protects against atherosclerosis via several mechanisms. It is a key mediator of reverse cholesterol transport, the process by which excess peripheral tissue cholesterol in lipid-laden macrophage-foam cells is shunted back to the liver for excretion. Additionally, HDL has anti-inflammatory, anti-oxidative, and anti-thrombotic activities that are suggested to contribute to its anti-atherogenic effects. The HDL in human plasma consists of several subpopulations of particles of distinct structure, composition and function. This heterogeneity, which is the result of continuous remodeling of HDL by plasma factors and specific membrane proteins such as ABCA1 and G1, has important implications in terms of the cardioprotective functions of HDL. Lipid modifying drugs, especially modern statins, have successfully been used for the treatment of high LDL cholesterol levels in several large-scale clinical trials. However, statin monotherapy may have its limits in the inhibition of the development of atherosclerosis. Therefore, the treatment of CAD has recently been extended and targeted to low serum HDL cholesterol levels. However, elevated total HDL cholesterol levels may not reduce the progression of atherosclerosis as exemplified by a recent trial where the CETP inhibitor Torcetrapid failed to demonstrate reduction of atherosclerosis despite a large 50 % increase in HDL cholesterol levels. Considering the protective role of HDL it is of utmost importance to understand the formation of HDL as well as all the factors that modify the HDL subclass pattern. Our internationally recognized research programme has utilized various cohorts and characterized molecular mechanisms behind CAD. We have during the past ten years focused on several HDL-related aspects in atherosclerosis research, the major ones being: i) lipid transfer proteins, especially phospholipid transfer protein (PLTP) and its role in HDL metabolism, ii) inflammation as a risk factor in atherosclerosis, iii) role of HDL-associated estrogens in protection against atherosclerosis, and iv) characteristics of low and high HDL subjects: Finnish low-HDL families and Health 2000 Health Examination Survey material. At the departmental level, our expertise is being utilized to reveal the molecular mechanisms behind novel gene variants connected to dyslipidemias.

Regulation of cellular lipid homeostasis

Rapid methodological development in the field of lipid cell biology has enabled us to obtain the first glimpses on how the complexity of the cellular lipidome is generated and how it is intimately and delicately connected with the machineries that regulate functions such as vesicle transport, cytoskeletal dynamics, and signalling cascades responsible for cell proliferation, differentiation, and apoptosis. Lipidous signalling molecules including phosphoinositides, ceramide, lysophospholipids, sphingosine-related molecules, and oxysterols play key roles in these processes. Importantly, disturbances in these regulatory circuits are involved in the etiology of dyslipidemias, atherosclerosis, neurologic diseases, and possibly also cancer. The present activity aims to shed light on this area and has strong implications for both basic research and medicine.

Oxysterols, 27-carbon oxygenated derivatives of cholesterol, are potent regulators of cellular lipid metabolism. Their functions have been divided in three main categories: 1) control of gene expression, 2) role as intermediates in the biosynthesis of bile acids and steroid hormones and 3) sterol efflux from cells. The best known functions of these compounds thus involve the regulation of body sterol homeostasis. Oxysterols are highly enriched in macrophage foam cells within arterial walls and in atherosclerotic lesions. They have cytotoxic, pro-apoptotic, and pro-inflammatory activities, and facilitate the differentiation of monocytes into macrophages. Therefore, oxysterols have been suggested to adversely affect the development and stability of atherosclerotic lesions. However, the first protein identified that binds oxysterols was oxysterol binding protein, OSBP. It binds several oxysterols with high affinity to its carboxy-terminal ligand binding domain, and acts as a sterol sensor that integrates the cellular sterol status with sphingomyelin metabolism by regulating ceramide transport form the endoplasmic reticulum (ER) to the Golgi apparatus. Interestingly, OSBP also acts as a sterol-dependent regulator of extracellular signal regulated kinase (ERK) signalling pathways. Families of OSBP-related proteins (ORP) are found in eukaryotic organisms from yeast to man. Major activity in the group concentrates on characterizing the functional role of human ORP proteins in cellular lipid metabolism and membrane trafficking, as well as in the development of atherosclerosis.

The work in the group is well integrated with the activity in Matti Jauhiainen's group (see above); Work on cellular lipid homestasis closely tangents the study of HDL function. The group also acts as the cell biology expert center for the entire MLO department by providing help in methodology concerning cellular lipid metabolism and membrane trafficking.

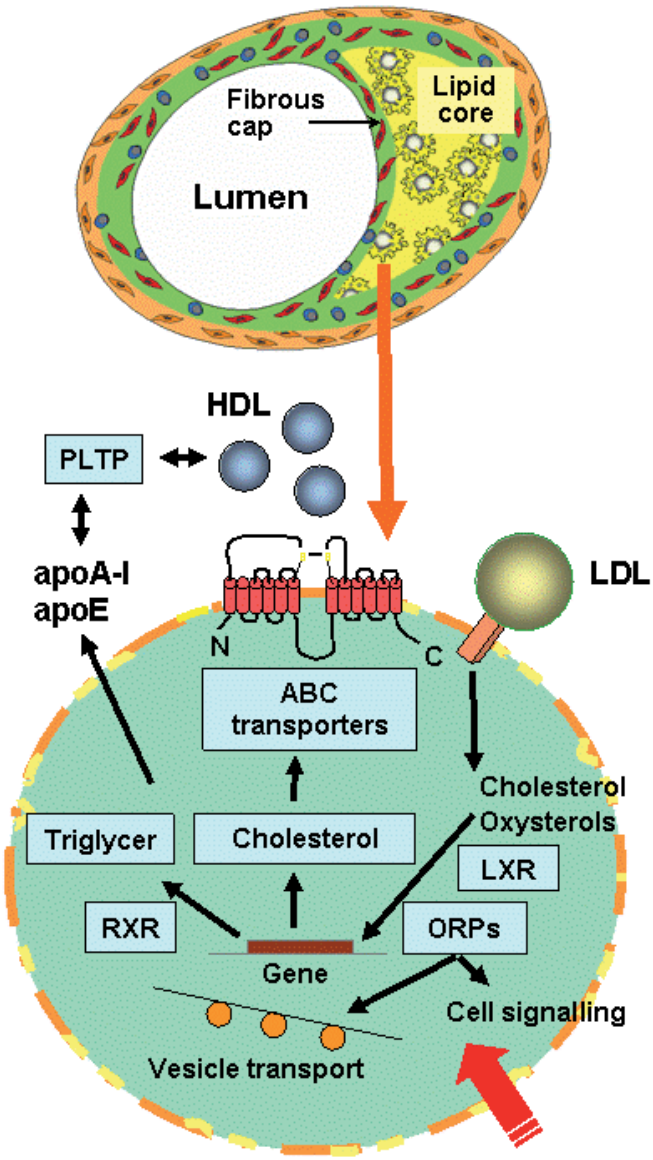

Figure 1. Research topics of the research program. The top image illustrates an atherosclerotic lesion, and the bottom image a cell, e.g. a macrophage foam cell, within the lesion. Central pathways and molecules with potential to modify lesion development are indicated in the cell image. Abbreviations: PLTP, phospholipid transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; apoA-I, apolipoprotein A-I; apoE, apolipoprotein E; ABC, ATP-binding cassette; LXR, liver X receptor; RXR, retinoid X receptor; ORP, oxysterol-binding protein related protein.

7.2. The main achievements

Participation in international epidemiological surveys

The research program has participated in three large international multicenter studies. These are the Diabetes Atherosclerosis Intervention Study (DAIS), the Fenofibrate Intervention and Event Lowering in Diabates (FIELD) Trial, and the European Multicenter Study on Familial Dyslipidemias in Patients with Premature Coronary Heart Disease (EUFAM). Representative of the research program was member of the steering

committees of the DAIS and FIELD studies, and acted as coordinator of the EUFAM study funded by the EU. In addition to the steering, coordination, and data analysis tasks performed by the research program, the Analytical Biochemistry Laboratory that belonged to the research program until 2001, performed a major share of the biochemical analyses of patient samples in all three studies.

Phospholipid transfer protein (PLTP): mechanisms of function and role in atherosclerosis

The regulatory role of PLTP in HDL metabolism is achieved via its two main functions, phospholipid transfer activity and the capability to modulate HDL size and composition in a process called HDL conversion. PLTP is capable of generating a specific subgroup of HDL, preβ-HDL through HDL conversion, and these particles have been suggested to participate in the removal of cholesterol from macrophage foam cells. On the other hand, PLTP may regulate HDL levels in the circulation due to its ability to transport surface remnants after lipolysis of triglyceride-rich lipoproteins like VLDL and chylomicrons. Thus, PLTP can be envisioned to play an important role in the prevention of atherosclerosis. Expression of the PLTP gene is subject to regulation by nuclear receptors. Bile acids regulate PLTP expression through farnesoid X receptor, FXR, and oxysterols through liver X receptors, LXR. It is conceivable that PLTP expression may represent an attempt to further boost processes of reverse cholesterol transport, in which PLTP is suggested to play an important role. The LXR targets, in addition to PLTP, include a number of genes with key roles in the reverse cholesterol transport and HDL metabolism, including cholesteryl ester transfer protein (CETP), ABCA1, ABCG1, and apoE.

PLTP seems to facilitate phospholipid transfer by acting as a true transfer protein between the donor (VLDL) and the acceptor (HDL) particles. In the second function associated with HDL conversion we have demonstrated that among the two lipid transfer proteins, PLTP is the major contributor to the generation of preβ-HDL particles *in vitro* and *in vivo* in a mouse model. During PLTP-mediated HDL conversion also large fused HDL particles are formed. Both preβ-HDL and large fused HDL particles enhance cholesterol removal from macrophages. In human plasma, PLTP exists in two forms, a high-activity (HA-PLTP) and a low-activity form (LA-PLTP). Using a subsample of the Health 2000 Health Examination Survey we showed that of the serum PLTP concentration, almost 50 % represented HA-PLTP. Altogether this population-based study revealed novel connections of the two PLTP forms not only to lipid but also carbohydrate metabolism. In addition to the antiatherogenic functions, PLTP may display also proatherogenic characteristics, and that these opposite features of PLTP could depend on the site of PLTP expression and action. We have shown that PLTP is present in human atherosclerotic lesions and is expressed by macrophages and foam cells. The role of macrophage-derived PLTP was investigated both in a macrophage cell culture system and in a mouse model. In a mouse model (bone-marrow transplantation technique), macrophage PLTP contributed significantly to total plasma phospholipid transfer activity but its deficiency in macrophages attenuated atherosclerotic lesion development. Similarly, macrophage CETP production in mouse promoted atherosclerotic lesion development. This data strongly suggest that the site of synthesis and function of the two lipid transfer proteins is important when assessing their role in atherosclerosis.

Inflammation as a risk factor in atherosclerosis

Since infection and inflammation are appreciated as novel underlying risk factors for atherosclerosis during the past decade, interest in candidate pathogens has grown. Certain pathogens are currently linked with the pathogenesis of CAD and atherosclerosis. Of these agents, *C. pneumoniae* is most strongly associated with atherosclerosis. *C. pneumoniae* has been identified in macrophages and within aortic intima and more recently, viable bacteria have been isolated from atherosclerotic plaques and abdominal aortic aneurysms. We have studied *C. pneumoniae* infection in a mouse model as well as using human material. A new sensitive and specific enzyme immunoassay method for the measurement of serum chlamydial lipopolysaccharide (cLPS) concentration was developed and applied to quantitate cLPS in sera of patients with acute coronary syndrome (ACS). During acute coronary syndrome, both cLPS and hsCRP were elevated. These findings suggest that cLPS is liberated from the damaged tissue persistenly infected with *C. pneumoniae* during the ACS event. In mouse studies we investigated whether *C. pneumoniae* infection is responsive to statin treatment. Pravastatin accelerated host response to *C. pneumoniae* infection, but unlike simvastatin, was not able to decrease infection load in the lungs. Our results in the Chlamydia project not only strengthen the association between *C. pneumoniae* infection and cardiovascular disease but also highlight the role of *C. pneumoniae* LPS in the inflammatory process during acute coronary syndrome.

Role of HDL-associated estrogens in protection against atherosclerosis

Risk for cardiovascular disease among premenopausal women is lower as compared to men of same age. However, the incidence of CAD in women increases markedly after natural or surgical menopause. The protective role of hormone replacement therapy against CAD is controversial as many observational studies have shown beneficial effects, but clinical trials have failed to show any cardiovascular risk reduction. Endogenous estrogens exert favourable effects by increasing HDL and reducing LDL levels and improving endothelial function. Our focus has been estrogen fatty acyl esters, a unique class of hormones that are water insoluble and carried lipoprotein-bound in circulation. Our data demonstrate that lecithin-cholesterol acyltransferase (LCAT) in circulation facilitates synthesis of estrogen fatty acyl derivatives, and major esterification occurs in the HDL_3 subfraction. The formed esterogen esters become incorporated in HDL particles where they protect the lipoprotein from oxidation. Estrogen esters can be transported to LDL in a process facilitated by CETP that could increase the anti-oxidative potential of LDL even after the particles have entered the vascular wall. This would ultimately hinder the foam cell formation. Current work indicates that HDL associated estrogen esters can be taken up at least via scavenger receptor B1 (SR-B1) into cells and the estrogen esters are hydrolyzed in the cell to generate free estradiol. Our data indicate that lipoprotein-bound estrogen fatty acyl esters, although existing at a low concentration level, may be physiologically important and affect the anti-atherogenic state in the cells to which HDL particles are targeted.

Characteristics of low and high HDL subjects

We have studied population-based samples utilizing the Health 2000 Survey study and Finnish low-HDL families. Our results suggest that the risk for the development of atherosclerosis measured as intima-media thickness in low-HDL family members is increased due to a decrease of HDL particle size and serum preβ-HDL concentration. Reduction of these HDL subspecies reflects a potentially efflux-deficient HDL pattern in the affected low-HDL family members. In addition, our recent data suggest that defective ABCA1 function in cholesterol-loaded macrophages is one potential

contributor to impaired reverse cholesterol transport process and the increased CAD risk in subjects with low HDL.

Identification and characterization of human oxysterol binding protein homologues

We carried out cDNA cloning and analysis of the gene structures of the entire human ORP family with 12 members. Thereafter, we have provided evidence for a role of OSBP and three ORPs, ORP1L, ORP2, ORP8, and ORP10 in cellular cholesterol and lipid metabolism, in endocytic membrane trafficking, in the development of atherosclerotic lesions in a mouse model, or in the control of human serum lipid levels. Our published data generated in collaboration with Dr. C.Thiele (Max-Planck-Institute, Dresden, Germany) suggests that at least 11 out of the 12 human ORPs bind 25-hydroxycholesterol (25OHC), cholesterol, or both. We modelled the structure of human ORP2, and verified by site-directed mutagenesis that the protein binds sterols within a pocket in the C-terminal ligand binding domain similar to that of yeast Osh4p, suggesting that ORPs throughout the eukaryotic kingdom share a similar fold. According to our working hypothesis, members of the ORP family sense the intracellular concentrations of different sterols and relay information to machineries responsible for the control of cellular lipid homeostasis, intracellular vesicle transport, and cell signalling.

Mechanisms of ORP function

The mechanisms of ORP function have been pursued mainly in cultured cell models. We have shown that ORP1L interacts with Rab7, a central regulator of the late endocytic pathway, and acts as an effector of the small GTPase. This interaction has strong impact on the microtubule-dependent sub-cellular distribution of late endosomes/lysosomes as well as the functional properties of these organelles. Furthermore, we have shown that Rab7, another Rab7 effector called RILP, and ORP1L form a tripartite complex that recruits the dynein-dynactin motor on late endosome membranes. ORP1L, which binds both sterols and phosphoinositides, most likely regulates the partitioning of the motor complex to membrane domains in which it can interact with its membrane anchor, spectrin.

ORP2 overexpression was found to have profound effects on the cholesterol metabolism in cell models, causing an increase of cellular cholesterol efflux and cell-type dependent effects on its storage in the form of cholesterol esters. The data suggests that excess ORP2 induces enhancement of intracellular cholesterol transport. Whether this involves function as a direct cholesterol carrier remains to be elucidated. ORP2 over-expression also leads to changes in the cellular phospholipid molecular species composition and a defect in neutral lipids (NL) and recycling of NL fatty acids. Our recent discovery of oxysterol-dependent localization of ORP2 on cytoplasmic NL droplets, and the finding that ORP2 silencing leads to increased triglyceride storage, suggest that ORP2 may execute a major function in NL metabolism. In an ongoing study we are, using site-specific mutants, assessing the specific roles of ORP2 sterol binding, NL droplet localization, and ER association in the functions of the protein in cellular cholesterol and NL metabolism.

In early 2006 we carried out in cultured cells a screen for ORPs that impact on the transcriptional regulation of cellular sterol homeostasis. Here, ORP8 came up as a promising candidate the overexpression and silencing of which had opposite effects on

the transcription of LXR and SREBP-2 target genes. ORP8 silencing was shown to induce upregulation of ABCA1 expression and cholesterol efflux to apoA-I, and its overexpression suppressed cholesterol biosynthesis. ORP8 was shown to bind 25OHC, to interact physically with SCAP, and to attenuate the enhancement of ABCA1 expression by oxysterols. The effects of ORP8 overexpression were shown to be dependent on sterol binding. However, it seems that the effects of ORP8 on ABCA1 are not dependent on LXR, suggesting that an entirely novel sterol-dependent regulatory pathway has been revealed. Importantly, ORP8 is abundant in macrophages, and elevated ORP8 expression is detected in human coronary artery atherosclerotic lesions, suggesting a role in cardiovascular diseases.

ORPs, lipid homeostasis *in vivo*, and atherosclerosis

We have employed new mouse models to cast light on ORP functions *in vivo*. These include a transgenic model that expresses human ORP1L under a macrophage-specific promoter, and adenovirus-mediated hepatic overexpression of OSBP, ORP1L, and ORP3. To reveal ORP functions in hepatic lipid metabolism, we determined the effects of adenovirus-mediated hepatic ORP overexpression in mice on serum and liver tissue lipids. OSBP expression was found to result in a strong elevation of both liver and serum VLDL triglyceride levels, due to up-regulation of SREBP-1c and its lipogenic target genes. This was connected with the down-regulation of extracellular signal regulated kinase (ERK) phosphorylation in the OSBP-transduced liver. Furthermore, we showed that silencing of OSBP expression by RNA interference in cultured hepatocytes suppressed the insulin stimulation of SREBP-1c expression and activity, as well as triglyceride synthesis. This study revealed a new, crucially important role of OSBP in the control of hepatic lipogenesis.

To approach ORP functions in the development of atherosclerosis we generated a transgenic (TG) mouse model expressing human ORP1L under a macrophage-specific promoter, that of scavenger receptor A. The mice were used as bone marrow (BM) donors to LDL receptor deficient animals, which were fed a Western-type diet. As compared to recipients of control bone marrow, the ORP1L BM recipients displayed a 110% increase of aortic root atherosclerotic lesion size. The TG macrophages displayed a decrease of ABCG1 and apolipoprotein E mRNA and protein levels, as well as impaired cholesterol efflux. Further, they displayed increased phospholipid transfer protein (PLTP) mRNA expression and activity in serum, all changes that provide explanations to the increased lesion size. ORP1L overexpression was shown to attenuate the stimulation of ABCG1 expression by the LXR agonist 22(R)-hydroxycholesterol, bringing up the possibility that the effects may be due to modulation of LXR activity. This work demonstrated for the first time the potential of ORPs as modulators of atherosclerosis and motivated further work to assess the role of the entire gene/protein family in cardiovascular diseases.

The analysis of linkage/association of ORP gene single nucleotide polymorphisms (SNP) with human dyslipidemias in collaboration with prof. L. Peltonen revealed linkage and association of certain ORP10 SNP alleles with HDL-cholesterol and TG levels in Finnish low-HDL and familial combined hyperlipidemia (FCHL) family materials. Functional characterization of ORP10 in order to clarify the mechanisms underlying the genetic findings is underway.

7.3. Scientific impact

Table 1. Summary of the scientific output during 1997-2007

Scientific output	**N**	**Comments**
Peer-review papers in international journals	201	In addition 36 review articles/book chapters. See Appendix 3
Invited lectures and chairmanships in international meetings	58	
Articles in domestic journals and text books	4	See Appendix 3
Lectures in domestic meetings and teaching lectures	60	
Editorial tasks in international journals	4	M.J., Clinical Chemistry and Laboratory Medicine; C.E., Current Opinion in Lipidology, CCLM, Atherosclerosis
Committee memberships: domestic	5	
Committee memberships: international (EU, WHO etc.)	6	
International evaluation panels (EU etc.)	9	
Organizing committee of international meetings	28	e.g. 76th Conference of the European Atherosclerosis Society, EAS, Helsinki, June 2007
Doctoral dissertations	13	See Appendix 3
Supervision of dissertations: ongoing	6	
Opponent of dissertations	13	
Pre-examiner of - dissertations - adjunct professors - professorships	 43 14 1	
Prizes	1	Aurator Asset Management Ltd (Turku, Finland) Stipendium in Research of Biotechnology and Medicine 2002 (V.O.)

7.4. Societal impact

Representatives of the Unit have served in the boards of foundations supporting research, the Finnish Atherosclerosis Society, the Finnish Society of Sciences of Letters and the Minerva medical Foundation, as well as consultants for the Medix Laboratories and Medix Biochemica Inc. The researchers have given a number of lectures at domestic scientific meetings (16) and, importantly, also layman lectures, e.g. to high school pupils and the senior citizens. Furthermore, information on lipid metabolism has been distributed to clinicians through articles published in domestic medical journals (5). Importantly, representative of the Unit has been member of the steering committee for Cardiovascular diseases and diabetes in the Health 2000 Health examination Survey.

Representatives of the Unit have also served in the executive boards of major international societies focusing on the basic and clinical aspects of atherosclerosis, the European Atherosclerosis Society (EAS) and the International Atherosclerosis Society (IAS), as well as in the council of Scandinavian Society for Atherosclerosis Research (SSAR) and European Lipoprotein Club.

7.5. Research funding

Table 2. Project funding during 1997-present

Project name	**Funding agency* (PI)****	**Funding k€**	**Years**
Antiatherogenic function of HDL	FO (MJ)	177	1997-2007
EUFAM	EU (CE)	420	1997-2000
FIELD study	CO (CE)	1 012	1997-2005
Role of PLTP in HDL metabolism	FO (CE)	200	2001-2004
Cholesterol removal from cells: role of transfer proteins and HDL-associated estradiol esters	FO (MJ)	69	2001-2007
Structure, function, and animal models of PLTP	FO (MJ)	151	2003-2007
Chlamydia pneumoniae and atherosclerosis	TEKES, SA (MJ)	23	2004-2006
PLTP: role in atherosclerosis	GS (MJ student)	56	2006-2009
PLTP: mechanisms of function and role in the reverse cholesterol transport process	SA (MJ)	180	2007-2009
Lipolytic and lipid transfer activities in the development of chicken ovarian follicles and the embryo	SA (JS)	180	2007-2009
Mechanisms of intracellular membrane trafficking	SA (VO)	217	1997-2000 2001-2003
Intracellular protein transport	EU TMR programme (VO)	205	1997-2000
Function of human OSBP-related proteins	SA (VO) SA (VO, ML)	1054	1999-2007
Human oxysterol-bind. proteins in lipid metabolism and atherosclerosis	FO (VO)	349	2000-2007
Integration of cellular lipid dynamics and signalling	SA (VO)	121	2000-2002
Functional analysis of the OSBP homologue ORP1L	GS (VO student)	105	2002-2005
Human oxysterol binding proteins	FO (VO)	34	2002, 2007
Oxysterol binding and PL transfer proteins	FO (VO)	57	2004-2007
Role of ORP2 in cellular lipid metabolism	GS (VO student)	56	2006-2009

*EU=European Union, SA=Academy of Finland, TEKES=Finnish Funding Agency for Technology and Innovation, FO=Foundations, CO=company. **PI=see senior scientific personnel in chapter 7.8

7.6. Scientific collaboration

Matti Jauhiainen

Antiatherogenic mechanims of HDL: structural, functional and clinical studies: Prof. Petri Kovanen (Wihuri Research Institute, Helsinki), Prof. Marja-Riitta Taskinen (University of Helsinki, Helsinki), Prof. Elina Ikonen (University of Helsinki, Helsinki), Acad. Prof. Leena Peltonen (KTL), Prof. Matti Tikkanen (University of Helsinki, Helsinki), Prof. Markku Savolainen (University of Oulu, Oulu), Adj. Prof. Mika Ala-Korpela (Technical University of Helsinki, Helsinki), Prof. Philip Barter (The Heart Research Institute, Sydney, Australia), Prof. Arie van Tol (Erasmus University, Rotterdam, The Netherlands), Prof. Kerry-Anne Rye (The Heart Research Institute, Sydney, Australia), Prof. Björn Dahlbäck (University Hospital, Malmö, Sweden), Prof. Jacques Genest (McGill University, Canada), Prof. Alice Lichtenstein (Tufts University, Boston, USA), Adj. Prof. Juha Holopainen (University of Helsinki, Helsinki), Prof. Wolfgang J. Schneider (Medical University of Vienna, Vienna, Austria).

Vesa Olkkonen

Role of OSBP-related proteins (ORP) in lipid metabolism and in the development of athetrosclerosis: Dr. Gerd Wohlfahrt (Orion Pharmaceutical Corporation, Espoo, Finland), Prof. Seppo Ylä-Herttuala (AIV-Institute, University of Kuopio, Finland), Prof. Petri Kovanen (Wihuri Research Institute, Helsinki, Finland), Acad. Prof. Leena Peltonen (KTL), Dr. Christoph Thiele (Max-Planck-Institute of Molecular Cell Biology and Genetics, Dresden, Germany), Prof. Bart Staels (Pasteur Institute, Lille, France), Dr. Andrew Brown (University of New South Wales, Sydney, Australia), Dr. Miranda van Eck (Leiden/Amsterdam Center for Drug Research, Gorlaeus Laboratories, Leiden, The Netherlands), Prof. Jacques Neefjes (The Netherlands Cancer Institute, Amsterdam, The Netherlands)

7.7. Proposal for the future work and expected (societal) benefits (next five years)

During the next five years the research programme will focus on: 1) The anti-atherogenic mechanisms of high-density lipoproteins, 2) The role of fasting-induced adipose factor (FIAF) in regulation of lipoprotein metabolism, 3) The relationship between inflammation and atherosclerosis, 4) New regulatory mechanisms integrating the cellular sterol status with metabolism of other lipid classes and with signalling processes, 5) The role of OSBP-related proteins and their interaction partners in the complex genetic background of common diseases. Additionally, we will contribute to the biotechnology strategy of KTL by 6) Development and utilization of new approaches and methods which allow maximal extraction of relevant information from the nationwide epidemiologic population cohorts. The projects are outlined below in more detail.

1) The mechanisms by which anti-atherogenic preβ-HDL are generated are poorly known. To elucidate the interplay between phospholipid transfer prorein (PLTP) and the new apolipoprotein, apoM, and its importance for HDL metabolism, we will utilize apoM mouse models and subsamples from different epidemiological cohorts. Furthermore, we aim to gain a more clear definition of the mechanisms by which structural modifications of HDL, PLTP and CETP by proteolytic and lipolytic enzymes present in the arterial intima modify their function in the reverse cholesterol transport. We believe that prevention of these proteolytic processes would significantly decelerate atherogenesis, and thus prevent atherothrombotic complications such as premature myocardial infarction. A second HDL-related research topic is the mechanisms of HDL-associated estrogens in protection against atherosclerosis. The future research aims to

investigate in detail the receptor-associated pathways of cellular uptake of HDL-associated female hormone estradiol and its fatty acyl derivatives. Moreover, the mechanisms of intracellular hydrolysis of the estradiol esters to generate biologically active, free estrogen will be investigated. This will further add to our knowledge of the antiatherogenic abilities of estrogen and HDL.

2) Obesity is currently a major public health problem. At least one out of five obese people develops type 2 (adult-onset) diabetes, and many more develop abnormalities of carbohydrate metabolism called impaired glucose tolerance, a pre-diabetic state. One group of recently emerged factors having a major impact on lipid and possibly glucose metabolism are the ANGPTL (angiopoietin-like proteins). Our aim is to study one of these, Fasting-Induced Adipose Factor, FIAF. The composite literature data suggest that via physical association with plasma lipoproteins, FIAF acts as a powerful signal from fat and other tissues to prevent fat storage and stimulate fat mobilization, especially under conditions of fasting. This suggests that disturbance in FIAF signalling might be involved in dyslipidemia. We will develop a realiable method for quantification of FIAF in plasma samples and determine the response of FIAF levels to fibrate treatment. Furthermore, we will study whether changes in lipoprotein profiles and other clinical parameters correlate with changes in FIAF levels. The study material is the Finnish arm of the FIELD study, and a subsample of the Health 2000 Health Examination Survey is used as “normal” population.

3) We will, as a large collaborative effort, clarify the role of periodontal pathogens and *C. pneumoniae* as risk factors for cardiovascular diseases. Animal models and human samples will be used to analyze lipoprotein levels and degree of atherosclerosis. It has been suggested that chronic infections may have a role in both the initiation and progression of atherosclerosis. So far only single pathogens have been studied as risk factors for CAD. However, the frequency of *C. pneumoniae* and oral pathogen infection in Finland is rather high. For this reason it is important to study their combined effect in atherosclerosis since there may be differences launched by them for instance in the degree of liver steatosis, dyslipidemia, and inflammation signalling. We expect to reach break-thoughs in understanding the role of chronic inflammation in the development of atherosclerotic cardiovascular diseases.

4) To gain insight into the novel regulatory pathways that OSBP-related proteins (ORPs) form part of, we will create animal models in which expression of ORPs is silenced, or genes encoding the proteins are disrupted. Here, we aim to clarify the roles of these proteins especially in hepatic lipid metabolism and in macrophages. Simultaneously with the animal model work, cell models are employed to investigate (i) the individual ORP functions and (ii) the effects of simultaneous silencing of multiple ORPs, which are likely to execute partially overlapping tasks. The phenotypic analysis of the models focuses on lipid metabolism, gene expression analysis, and functional assays monitoring intracellular vesicle transport and signalling cascades. Special effort is invested on identifying connections between the ORP effector pathways and the signalling pathways playing central roles in obesity, type 2 diabetes, and atherosclerosis.

5) We aim to elucidate the role of OSBP-related proteins and other components in their effector pathways, in the complex genetic background of common lipid disorders and atherosclerosis. The linkage and association of SNP polymorphisms in these genes with serum lipid parameters and other clinical

phenotypes will be investigated. The genetic studies are complemented by functional analysis in relevant cell and animal models. As the ultimate goal, we aim to elucidate the possibilities of using these novel factors as targets for the development of new therapies to prevent and treat dyslipidemias, atherosclerotic cardiovascular diseases, and type 2 diabetes.

6) In all of the above projects we will maximally utilize the nationwide epidemiological cohorts. Furthermore, we aim to develop new approaches and methods which allow maximal extraction of relevant information from the population cohorts by using modern technologies. As an example, we have successfully started a collaboration in which NMR metabonomics is applied to analyze plasma lipoprotein subclasses. This high-throughput method will be used to make clinically relevant lipoprotein subclass profiles available for use e.g. in the evaluation of an individual's risk for coronary heart disease.

7.8. Senior scientific personnel

Christian Ehnholm, M.D., Ph.D., research professor 1977-2005, Emeritus Professor 2005-
Matti Jauhiainen, Ph.D., adjunct professor, group leader 1988-
Vesa Olkkonen, Ph.D., adjunct professor, group leader 1993-
Elina Ikonen, M.D., Ph.D., adjunct professor, group leader 1997-2004
Jouko Sundvall, M.Sc., head chemist, analytical biochemistry 1997-2001
Marjatta Antikainen, M.D., Ph.D., senior investigator 1997-1999
Markku Lehto, Ph.D., senior investigator 1999-2007
Daoguang Yan, M.D., Ph.D., senior investigator 2005-2007
Julia Perttilä, Ph.D., post-doctoral fellow 2006-
Jani Saarela, Ph.D., post-doctoral fellow 2007-

7.9. 15 key references

Article	IF	No of citat.*
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Vehkavaara S, Hakala-Ala-Pietila T, Virkamaki A, Bergholm R, Ehnholm C, Hovatta O, Taskinen MR, Yki-Jarvinen H. Differential effects of oral and transdermal estrogen replacement therapy on endothelial function in postmenopausal women (2000) *Circulation,* 102:2687-93	**11.632**	**51**
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Yan D, Jauhiainen M, Hildebrand RB, Willems van Dijk K, Van Berkel TJ, Ehnholm C, Van Eck M, Olkkonen VM. Expression of Human OSBP-Related Protein 1L in Macrophages Enhances Atherosclerotic Lesion Development in LDL Receptor-Deficient Mice (2007) *Arterioscler Thromb Vasc Biol,* 27:1618-24	**7.053**	**-**

* based on Web of Science August 2007

8 PATERNITY TESTING LABORATORY

Mission and personnel of the laboratory

Paternity testing laboratory performs paternity and other related testing applying reliable, up-to-date and quality controlled DNA-based methods. We aim to direct our services to satisfy our customer's needs and constantly improve the quality of our work. At present the personnel consists of four full time and one half time workers. The head of the laboratory is M.Sc. Matti Lukka. In addition three of the researchers of MLO work part-time in PTL (Ismo Ulmanen, Marjo Kestilä, Pekka Ellonen).

Legal framework

The official paternity testing is based on the paternity law from 1975 and on the law on forensic genetic paternity testing and additional statutes from 2005. Based on this legislation paternity testing is performed, if necessary, to establish the paternity for a child born out of marriage or in the cases of annulment of paternity. The law from 2005 states that paternity testing is based on genes, inherited DNA or gene products. Moreover the law rules that if the father candidate is dead, or cannot be reached, his parents or other relatives can be tested. According to the 2005 law the official paternity testing is carried out in PTL of National Public Health Institute or in Department of Forensic Medicine, University of Helsinki. In addition the law on alien immigrants from 2000 orders that the biological relatedness within immigrating families is verified by testing in PTL or in Department of Forensic Medicine, University of Helsinki.

Volume of paternity testing in 1997-2007

During the inspected period of time the number of investigated paternity cases has increased from about 1100 to about 1400 cases per year. About 75 percent of the investigations are ordered by municipal child welfare officials. Our next biggest customers are private persons and courts. The proportions of different customer categories have stayed rather stable. The number of other relatedness testing but direct paternity was about 30 in 2006.

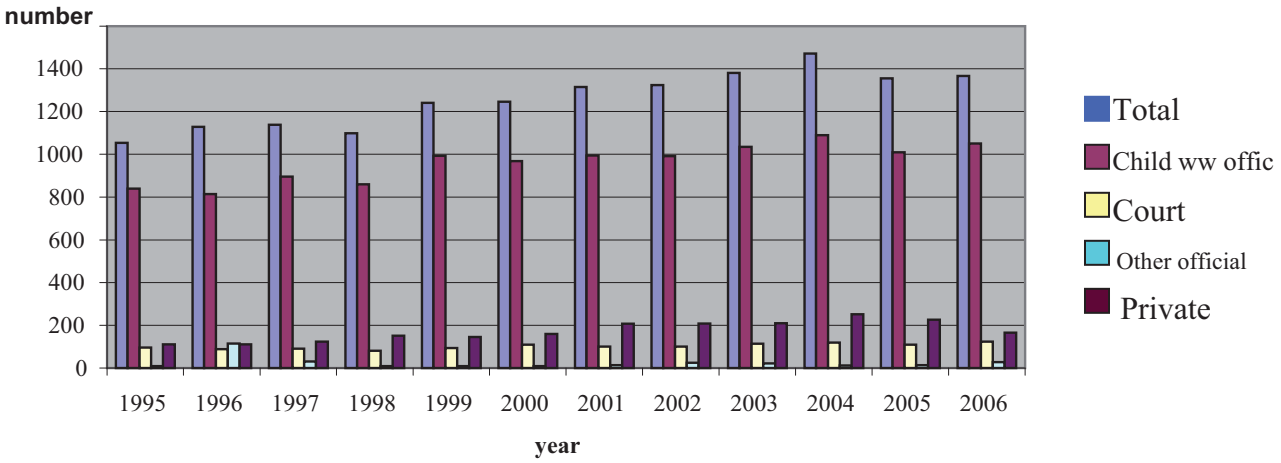

Figure 1. Development of the paternity cases analysed in the PTL starting from 1995 to 2006. The numbers of cases are indicated according to the different categories of the customers.

Development of paternity testing methodology

The methodology of testing in PTL has been based on PCR amplification of short tandem repeat (STR) DNA. Since year the 2000 the electrophoretic separation of DNA fragments has been performed, instead of gel electrophoresis, by using ABI310 capillary electrophoresis equipment. Four commonly used commercial DNA-marker kits have been introduced as they have come to market. Our analysis resources of today are composed of 19 autosomal and 12 Y-chromosomal STR DNA-markers.

Development of quality

Paternity testing laboratory has been accredited since 2002. Accreditation is based on internationally agreed criteria and it's goal is to recognize a body's competence to carry out specific tasks. When the laboratory is accredited clients can trust that the independent third part has evaluated the activities and found them to be competent, reliable and credible. In Finland accreditation is performed by FINAS (Finnish accreditation service) and it carries out assessments annually. The purpose of assessments is to consolidate the quality management and technical competence and encourage the continuous development of their activities. Scope of accreditation in paternity testing laboratory is paternity testing in forensic genetics, including DNA isolation, DNA amplification and DNA typing. PTL also participates in the yearly international quality control test carried out by the English Speaking Working Group of International Society of Forensic Genetics.

Scientific and international activities

The goal of the PTL is and has been to follow and participate scientific and international activities in the field of forensic genetics. During 1997-2007 period the researchers of the laboratory have published four scientific reports. The laboratory personell participate actively the events, like meeting and courses, of the International Society of Forensic Genetics (ISFG). In 2006 PTL personell arranged together with Dept. of Forensic Genetics, University of Helsinki, the international conference on forensic genetics in Tuusula, Finland. This was one of the main international events of the field in 2006 and was attended by 100 participants from 28 different countries.

Paternity testing in the future

It is most likely that the present paternity testing methodology, applied also in PTL, will be based on PCR of STRs at least in the near future. However, the laboratory processes will be developed to be more automated. The DNA marker resources and calculation methods will be further developed to produce information more effectively in the complicated paternity and kinship cases. We predict that the volume of paternity testing is likely to rather increase than to decrease in the near future.

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9 APPENDIXES

Appendix 1: The Finnish disease heritage - Dissertations and publications in 1997-2007

Dissertations 1997-2007

1. Aaltonen J: Molecular genetics of APECED (Autoimmune PolyEndocrinopathy Candidiasis Ectodermal Dystrophy). 1998. (Publications of National Public Health Institute A3/1998)
2. Klockars T: Positional cloning of the CLN5 gene. 1998. (Publications of the National Public Health Institute A22/1998)
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Appendix 2: Genetic epidemiology - Dissertations and publications in 1997-2007

Dissertations 1997-2007

1. Hovatta I: Molecular genetics of familial schizophrenia and PLO-SL. 1998. (Publications of the National Public Health Institute A20/1998)
2. Pekkarinen P: Genetic mapping of the loci for a monogenic and a multifactorial neuropsychiatric disorder: PLO-SL and familial bipolar disorder. 1998. (Publications of the National Public Health Institute A19/1998)
3. Kuokkanen S: Search for gene loci predisposing to multiple sclerosis in the Finnish population. 1998. (Publications of the National Public Health Institute A13/1998)
4. Lönnqvist L: Molecular genetics of type I fibrillinopathies. 1998. (Publications of the National Public Health Institute A16/1998)
5. Pajukanta P: Search for familial combined hyperlipidemia susceptibility genes. 1998. (Publications of the National Public Health Institute A26/1998)
6. Rantamäki-Häkkinen T: Fibrillin defects in Marfan syndrome: impact on DNA diagnosis and molecular pathogenesis. 1998. (Publications of the National Public Health Institute A5/1998)
7. Perola M: Finnish genes of hypertension. 1999. (Publications of the National Public Health Institution A8/1999)
8. Kaukonen J: Autosomal dominant progressive external ophthalmoplegia (adPEO): A tale of two genomes. 2000. (Publications of the National Public Health A4/2000)
9. Pastinen T: Scoring human genomic SNPs and mutations: multiplexed primer extension with manifolds and microarrays as solid-support. 2000. (Publications of the National Public Health Institute A5/2000).
10. Ekelund J: Molecular genetics of schizophrenia and comorbid and related traits. 2001. (Publications of the National Public Health Institute A17/2001).
11. Öhman M: The Search for genes predisposing to obesity. 2001. (Publications of the National Public Health Institution A3/2001)
12. Auranen M: Molecular genetics of autism spectrum disorders in the Finnish population. 2002. (Publications of the National Public Health Institute A23/2002)
13. Chen D: Identification of Gene Variations on Chromosome 17 Associated with Multiple Sclerosis. 2003. (UCLA David Geffen School of Medicine and the National Public Health Institution)
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15. Bronnikov D: Identification of multiple sclerosis susceptibility genes in Finnish Population. 2005. (UCLA David Geffen School of Medicine and the National Public Health Institution)
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17. Enattah N: Molecular Genetics of Lactase Persistence. 2005. (Publications of the National Public Health Institute A4/2005)
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19. Suviolahti E: Search for genetic variants conferring the susceptibility to obesity and related metabolic traits. 2005. (Publications of the National Public Health Institution A25/2005)
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Domestic articles

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2. Pajukanta, P. and Palotie, L. (1998) [Genetics of hereditary dyslipidemia now becoming clear]. *Duodecim,* 114, 1447-1449
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4. Kontula, K., Perola, M., Hiltunen, T., Kainulainen, K. and Palotie, L. (2000) [Genes and hypertension]. *Duodecim,* 116, 1751-8
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5. Palotie, L. (2002) Ihmisen perimän kartoitus. *Perinnöllisyyslääketiede,* 65-76
6. Palotie, L., Palotie, A. (2007) Geenikartoituksesta tautien syiden ymmärtämiseen. *Perinnöllisyyslääketiede*, 48-59

Appendix 3: Molecular biology of cardiovascular diseases - Dissertations and publications in 1997-2007

Dissertations 1997-2007

1. Pussinen P, Plasma phospholipid transfer protein (PLTP) in high density lipoprotein (HDL) metabolism. 1997. (Publications of the National Public Health Institute A7/1997)
2. Huuskonen J: The phospholipid transfer activity and structural features of human plasma PLTP. 1999. (Publications of the National Public Health Institute, A5/1999)
3. Riento K: Characterization of Munc-18-2, a Mammalian Sec1 Protein. 1999. (The Publications of the National Public Health Institute A13/1999)
4. Jaari S: Proteins involved in high density lipoprotein metabolism. 2002. (Publications of the National Public Health Institute A1/2002)
5. Laitinen S: Family of human oxysterol binding protein homologues: ORP2 is a new regulator of cellular lipid metabolism. 2002. (Publications of the National Public Health Institute A12/2002)
6. Blom TS: Characterisation of cellular defects in Niemann-Pick type C disease. 2003. (Publications of the National Public Health Institute A6/2003)
7. Heino S: Transport of newly synthesized sterols to extracellular acceptors. 2003. (Publications of the National Public Health A5/2003)
8. Kauppi M: Functional characterisation of Rab22a and Munc18B, two proteins regulating vesicle transport in mammalian cells. 2004. (Publications of the National Public Health Institute A4/2004)
9. Höckerstedt A: Estradiol fatty acid esterification in high density lipoprotein. 2004. (ethesis.helsinki.fi)
10. Siggins S: Plasma Phospholipid ransfer Protein (PLTP): quantitation, biosynthesis, and involvement in hepatic lipid homeostasis. 2005. (Publications of the National Public Health Institute A16/2005)
11. Johansson M: ORP1L, a new Rab7 effector and regulator of late endosome functions. 2006. (Publications of the National Public Health Institute A7/2006)
12. Jänis M: The high- and low-activity forms of human plasma phospholipid transfer protein (PLTP). 2006. (Publications of the National Public Health Institute A12/2006)
13. Tiirola T: Effects of *Chlamydia pneumoniae* infection on inflammation and lipid parameters in humans and mice. (Publications of the National Public Health Institute A14/2006)

Publications 1997-2007

International peer review articles

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11. Lindberg, O., Tilvis, R.S., Strandberg, T.E., Valvanne, J., Sairanen, S., Ehnholm, C. and Tuomilehto, J. (1997) Impacts of components of the metabolic syndrome on health status and survival in an aged population. *Eur J Epidemiol,* 13, 429-34. 1.361
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INTERNATIONAL EVALUATION OF THE DEPARTMENT OF MOLECULAR MEDICINE NATIONAL PUBLIC HEALTH INSTITUTE FINLAND

EVALUATION REPORT

26.9.2007

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PREAMBLE

Introduction

The mission of the National Public Health Institute (KTL) in Finland is to protect and promote the health of the Finnish people. As a research and expert institute belonging to the Ministry of Social Affairs and Health, KTL is responsible for providing decision-makers, professionals and citizens with the best possible health-related information for their choices. A general strategy for the Institute was prepared in 2001, while detailed objectives for the work are agreed upon annually with the Ministry. Ultimate responsibility of leading and managing the whole Institute rests on the Director General of KTL. The three main areas of work in KTL have traditionally been: 1) infectious diseases and immunizations, 2) chronic diseases and health promotion, and 3) environmental health. In all these areas, both research and public health functions are carried out. Activities of the Institute include basic research, ranging from detailed analysis of the molecular mechanisms of pathogenesis to large scale epidemiological and preventive studies and research into factors influencing health.

KTL's main facilities are located in Helsinki and three other facilities in Kuopio, Oulu and Turku. The Institute with the total personnel of 980 has 12 departments, each of which is built of various laboratories and units. The Department of Molecular Medicine of KTL is located in Helsinki. It lists as its goals characterization of the molecular background of human diseases and production of new data on the relationship between the genetic and life style risk factors that result in the health problems of Finns. Current research programs of the Department focus on the characterization of the molecular background of the Finnish disease heritage, cardiovascular diseases, genetic epidemiology of common diseases and systems biology.

The task of the Evaluation Panel

The objective of the review was to provide an evaluation of the work of the Department of Molecular Medicine of KTL for the Ministry of Social Affairs and Health. The evaluation was to examine the functions, strategic importance, scientific merits and value for money of the scientific and expert work undertaken, and to make proposals for future work. A special emphasis was to be placed on the evaluation of the relevance and effectiveness of the work and of its impact on the health of Finnish people.

Composition of the Evaluation Panel

The Evaluation Panel consisted of Professor Albert Hofman (Erasmus MC, Rotterdam, The Netherlands), Professor Alan Wright (MRC Human Genetics Unit, Edinburgh, UK), Professor Mart Saarma (University of Helsinki, Helsinki, Finland) and Chancellor Eero Vuorio (University of Turku, Turku, Finland), who acted as the Chair of the Panel.

1 REVIEW OF THE ACTIVITIES OF THE DEPARTMENT OF MOLECULAR MEDICINE (MLO)

1.1. Background information

The current department of Molecular Medicine is a result of a merge of two previous departments of KTL: Department of Human Molecular Genetics and Department of Biochemistry. This administrative reconstruction was based on the recommendation by the previous international evaluation of 1995, and took place in 2001. Since June 1, 2007 the research programs and core facilities of MLO were strategically joined as a part of the Institute for Molecular Medicine Finland (FIMM). At the same time the Paternity Testing Laboratory was integrated into the Department of Research and Expertise Support Services.

Department of Human Molecular Genetics (founded in 1988, Director Professor Leena Peltonen) exploited the unique opportunities of the genetic isolation of Finland to analyse the genetic background of human disease. The main goal of the department was to characterize the molecular background of the diseases of Finnish disease heritage and via this effort to develop tools and analytical strategies for the identification of genetic and life style risk profiles in common multifactorial diseases, representing public health problems. Additionally, the department developed specific DNA test panels of disease mutations based on findings made in population based studies. The department served investigators both within KTL and nationwide as a knowledge centre for human genetics-related molecular biology techniques. Unlike the other Departments at KTL, the main mission of the Department of Human Molecular Genetics was research and it had no public health responsibilities beyond being in charge of the DNA-based national paternity testing.

The 1995 Evaluation Panel concluded that the department had exploited effectively the Finnish disease heritage and in the field of common diseases had produced studies of the highest standard, especially in multiple sclerosis and bipolar disease. Specifically, this was attributed to the good collaborations with the FINRISK study and the Department of Mental Health. The research in human genetics was considered of major potential significance for public health. The panel recommended that (i) there should be further investment in this group in view of the potential public health importance of research in human genetics, (ii) the KTL should consider developing mechanisms through further investment in collaborations to extend the range of studies on the structure and function of gene products, including the use of transgenic animals and (iii) these studies should be developed further through the development of screening and other programmes – particularly through collaborations with other groups in KTL which have the necessary skills in epidemiology and behavioural sciences.

Department of Biochemistry (which functioned until 2001 under the directorship of Professor Christian Ehnholm) has concentrated on three major research topics: Lipoprotein metabolism, lipoprotein genetics and cell biology. The major focus was on lipoprotein metabolism and genetic factors influencing the risk of cardiovascular disease. The cell biology research was directed to the study of intracellular membrane traffic and microsomal triglyceride transfer. The department was specialized also in extensive biomarker analyses of lipid metabolism supporting research projects nationwide. In the 1995 Evaluation Report the research on lipoprotein metabolism was considered of high

quality and the lipoprotein genetics of good quality. The quality of the cell biology research was considered impressive. The panel recommended that (i) a strategic reappraisal of the role of the KTL in cardiovascular research should be undertaken covering particularly the departments of Epidemiology and Health Promotion, Human Molecular Genetics, Nutrition and Biochemistry with possibly some reconfiguration of departmental boundaries to meet the needs of the strategy more effectively and enhance critical mass in the key areas, and that (ii) the professional staff of the Department should be encouraged to develop their own high quality research programmes within an overall strategic framework; and that (iii) the cell biology group should be strengthened.

Department of Molecular Medicine (MLO) was founded in 2001 by merging the Departments of Human Molecular Genetics and Biochemistry. The first director was Christian Ehnholm (2001-2002), followed by Leena Peltonen (2002-2004) and Anu Jalanko (2004-). The MLO moved to the new biomedical research building: Biomedicum Helsinki, located on the Meilahti medical campus housing preclinical departments of the Medical Faculty of the University of Helsinki, next to the University Hospital. The research activities of the MLO have been since organized into programmes that were identified as the most relevant areas from the public health and scientific perspectives.

1.2. Department of Molecular Medicine today

Organization. The department consists of three research programs (Genetic Epidemiology, Finnish Disease Heritage, and Molecular Biology of Cardiovascular Diseases) with eight research groups) and three core facilities (Large Scale DNA Extraction and Storage Facility, Bioinformatics and Biotechnology). Until 31.5.2007 the Paternity Testing Laboratory was also part of the MLO. Since June 1, 2007, the research programs and core facilities of MLO have been strategically joined as a part of the Institute for Molecular Medicine Finland (FIMM), which signed (together with similar institutes in Umeå, Sweden, and Oslo, Norway) a partnership agreement with European Molecular Biology Laboratory (EMBL) on Oct 3, 2007.

Research programme on genetic epidemiology (Programme Director Leena Peltonen)

The research programme on genetic epidemiology is based on the access of KTL to well defined Finnish study samples including large pedigrees of specific diseases and nationwide epidemiological cohorts. The major research projects involve molecular characterization of hyperlipidemias, metabolic syndrome, multiple sclerosis and severe psychiatric disorders. Utilization of genome-wide marker maps, transcript analyses combined with new tools in biocomputing and biostatistics has resulted in the initial identification of several genes and loci associated with common diseases. This success is based on efficient use of the special population structure of Finland and has provided new paradigms for the use of founder populations in disease gene identification. This research area has also remarkably contributed to the development of new technologies for the collection and analysis of massive genome-wide information.

The **systems biology** research area was initiated within the Genetic epidemiology programme of the MLO with the recruitment of Professor Jussi Taipale in 2005. J. Taipale has the joint appointment from the KTL and the University of Helsinki. The

research of his group aims at understanding disease mechanisms and development of high content screening methods to facilitate identification of new cancer disease genes and characterization of the functions of genes and their regulatory elements. Development of novel methodologies has already resulted in internationally recognized success.

Research programme on the molecular biology of cardiovascular diseases (Programme Director Matti Jauhiainen)
The genetic findings in lipid metabolism constitute the basis for the functional analyses aimed at understanding the molecular mechanisms behind cardiovascular diseases. This research area utilizes biochemical, cellular and animal models to tackle basic lipid metabolism. Life style and nutritional risk factors are tackled utilizing nationwide sample cohorts and functional analyses.

Research programme on Finnish disease heritage (Programme Director Marjo Kestilä)
The Finnish disease heritage consists of over 30, typically recessive inherited diseases, enriched in this founder population. They have provided a proof of principle for the efficient use of the unique population structure and sample resources in identification and characterization of disease genes, development of DNA-based diagnostics and elucidation of metabolic pathways important for human health in general. This research utilizes cell and animal models and genome-wide functional analyses to follow the disease process in cells and tissues.

Core facilities and technology platforms
Most of the core facilities and technology platforms have been developed in a close collaboration and by joint funding with the University of Helsinki/Biomedicum Helsinki. This activity of KTL is a wonderful example of the fruitful collaboration between the institutions working under different ministries. Many of the key scientists working in the core facilities have also joint appointments at the KTL and University of Helsinki. KTL and Biomedicum Helsinki are to be congratulated for their success in the development of these very important units. It is important to note that MLO scientists working at Biomedicum Helsinki have free access also to other important core facilities at the University of Helsinki. These include various imaging techniques, protein chemistry, electron microscopy etc. In addition, KTL scientists have also used the services of the Finnish Genome Centre that has currently been fused with the FIMM.

The bioinformatics unit (Head Juha Saharinen) utilizes and develops genome-wide computational analyses for the research purposes of molecular medicine.
The biotechnology core facility (Head Janna Saarela) develops and provides easy access for investigators to genome-wide methods in transcript profiling and characterization of copy-number and functional variations using DNA microarray technology. ***The DNA sequencing facility*** **(Project manager Pekka Ellonen)** is part of the biotechnology core offering high quality sequencing and genotyping services for the research community also outside KTL.
Large Scale DNA Extraction and Storage Facility/National Biobank of Finland (Project manager Päivi Laiho) serves the research groups of KTL and universities in DNA biobanking. It is equipped with state of the art sample tracking system, automated DNA extraction equipment, liquid handling robots, storage facilities and data management tools for sample logistics and optimal confidentiality and quality control.

This core facility is a joint operation of KTL, FIMM and several Finnish and foreign collaborators (universities, hospitals and national public health institutes).

As its goal the Department of Molecular Medicine lists the use of the unique Finnish study samples and population cohorts to characterize the molecular background of human diseases. This includes efforts to produce new data on the relationship between the genetic and life style risk factors that result in public health problems. The resulting genome-wide information is further utilized to develop intervention strategies and more biology-related classification for diseases, which are potentially valuable for developing diagnostics. The research programs are especially focused on characterization of the molecular background of Finnish disease heritage, cardiovascular diseases and neuropsychiatric diseases. The Department provides expertise in a wide range of genomic and biocomputational analyses for the national and international scientific community, for national health care officials, for decision makers and for the general public.

To guarantee its top level of expertise in modern genetic and biological analyses, MLO has built an infrastructure that facilitates the collection of genome-wide information on the genetic background of diseases as well as functional information on the molecules that are critical in the disease process. Furthermore, the department has established necessary database and computational resources for the expert analyses of the massive amount of collected biological information. MLO reports that its scientific expertise, technology platforms and large nationwide sample collections facilitate a highly competitive environment for research and education in molecular medicine for the 21st century.

1.3. Staff and resources

The development of personnel of the MLO has increased steadily from 1997 to 2007, and currently comprises 44 permanent and 139 externally funded positions. The annual governmental budget has varied between 1.6-2.7 million euros including also the salaries of the permanent personnel (currently 2.06 million euros), and the external funding has increased from 0.6 million euros in 1997 to a stable 2.6 million euros, which represents 55% of the total funding including rents and equipment, but excluding internal services (management help, animal facility support, media kitchen, library services).

1.4. Strategic planning and management

The Director General of the KTL distributes the overall resources between departments after acceptance of the annual strategic plan of each department. The steering group of MLO (program leaders and core facility leaders) meets the Director General once a year to present the yearly achievements and strategic plans for the next year. The internal allocation of resources takes place upon the acceptance of the strategic plan and the Director General does not interfere with the internal allocation of resources. At the beginning of each year the director of the Department makes a proposal for the allocation of the institutional funds to the steering group of the Department that provides feedback and then the budget is finalized by the Department director. Once a year, the steering group of MLO holds a strategic brainstorming session to discuss

future developmental needs of the Department. All research programs have their own strategy days also at least once a year.

The steering group of the Department meets once a week to discuss urgent matters and plans. MLO has a weekly departmental meeting for all personnel, at which the director of the Department briefly informs everyone about important current issues. These meetings also contain presentations by invited lecturers, and by postdoctoral and junior researchers of the MLO. These monthly meetings end with a free discussion on pertinent scientific and administrative matters. The meetings are held in English to facilitate participation of the non-Finnish speaking scientists.

Each research program has a weekly meeting on managerial subjects. In these meetings the research progress of each project is followed thoroughly. Research core facilities usually have their meetings once a month, assessing mostly managerial issues. Each core facility also has a supervisory group of scientists and stakeholders that meets at least once a year. Additionally, graduate students and postdoctoral researchers have regular strategic planning meetings with the supervisors and members of collaborating research groups.

As part of the new Finnish salary and support system, every employee has a discussion once a year with his/her supervisor where they discuss personal achievements, future plans, needs for further education etc. Additionally, salary agreement is discussed once a year between each employee and the immediate supervisor or unit head, within the limitations of the general rules of KTL and the budget available. To make the process transparent, the overall ranking of the different personnel groups are discussed in the Department board meeting.

2 SCOPE AND PURPOSE OF THE EVALUATION

The objective of the review was to provide an evaluation of the work of the Department of Molecular Medicine of KTL for the Ministry of Social Affairs and Health. The evaluation was to examine the functions, strategic importance, scientific merits and value for money of the scientific and expert work undertaken, and to make proposals for future work. A special emphasis was to be placed on the evaluation of the relevance and effectiveness of the work and of its impact on the health of Finnish people.

The evaluation and the Evaluation Report aimed to address the following main issues:

h.	National relevance and effectiveness of the activities
i.	Appropriateness and adequacy of the research, expert functions and services
j.	Output and quality of research activities
k.	National and international co-operation
l.	Resource allocation
m.	Research fund raising
n.	Development needs, especially regarding processes and organization

The evaluation panel was advised that the main purpose of the evaluation was to guide the Ministry of Social Affairs and Health in its strategic management of KTL. The

practical implementation of the results, based on the decisions made at the Ministry, is the responsibility of the Director General of KTL.

This evaluation is based on the written documentation provided for the panel prior to the site visit on September 26, 2007, and on the presentations given and interviews conducted during the site visit. The document prepared by Dr. Anu Jalanko, Director of the MLO, included 1) a report on progress in research over period 1997-2007 and research plans for the period 2007-2011, 2) the arrangement for governance and management, and 3) allocation of staff and resources, and 4) her plans for the future development of the Department. The document also included self evaluation of the Department regarding 1) the appropriateness of its work to the national public health needs, 2) its role in the dissemination of research results and knowledge and technology transfer, 3) a description of the interfaces between the Department and the key players in Finland and abroad. The panel was also informed of the Report of the 1995 Evaluation Panel of the National Public Health Institute. During the site visit panel members had an opportunity to interview group leaders, investigators and the staff of MLO and discuss with representatives of the University of Helsinki.

3 ASSESSMENT OF THE MLO BY THE EVALUATION PANEL

3.1. National relevance and effectiveness of the activities

The MLO section of KTL is in a unique position among biomedical research groups in Finland in that it is comparatively free of teaching or clinical commitments and can almost entirely focus on basic biomedical research. It can recruit good quality staff and students and has good core facilities, allowing it to make a disproportionate contribution to international research in molecular medicine. Only about 45% of its funding comes from the Ministry of Social Affairs and Health so that MLO researchers have competed well in obtaining external funds, which is reflected in their strong publication record, wide range of high quality collaborators and major success with EU program funding. At both national and international levels, they are in a good position to become even more effective by the formation of FIMM, formally linking scientists in MLO with others at the University of Helsinki and the University of Helsinki Hospitals, further strengthening the research infrastructure and links with clinical and academic medicine. Several individuals have shared professorships/adjunct professorships with other Institutions, indicating an existing high level of national integration, which is set to be strengthened further. We would therefore rate the overall effectiveness of MLO as very high, in both national and international contexts, in terms of value for money, research output and overall impact in molecular medicine.

Although the MLO has continued to fulfil its important role of developing novel approaches in biomedical research its role and achievements in implementing new biotechnologies, in patenting, licensing and technology transfer have been rather modest. In addition, although several findings at the Department have been published in top biomedical journals the Department has very little research and development agreements with domestic and international pharmaceutical and biotech companies. The Department has been an important environment for the development of talented individuals, but very few people have moved to biotech industry or started their own start-up companies.

3.2. Appropriateness and adequacy of the research, expert functions and services

The research output of MLO staff is very impressive, with a steady average of 50-60 publications per year, and mean impact factors of around 6. The standard is well maintained across the major MLO sections, namely the genetic epidemiology of common diseases, which produces about one-half of the above papers, the Finnish disease heritage and molecular biology of cardiovascular disease sections. The research activities of each section will be considered in more detail below (section 3). The expert functions of MLO staff are wide ranging, from international functions (HUGO, ESFRI, GenomEUtwin, UCLA, Broad Institute, Sanger Centre, Nordic Centre of Excellence) to national functions, such as the activities of the various Finnish population cohorts, provision of bioinformatic, sequencing, genotyping and microarray services for external researchers. In should be noted, however, that most of these contacts have been established and developed by Dr. L.Peltonen, whereas other senior researchers have been less active. Finally, the training of PhD students is a vital part of MLO activities which appears to be very successful. An average of about 6 PhD theses is completed per year, making an excellent and major contribution to training of the next generation of biomedical scientists. The committee met with the graduate students and found them to be quite satisfied with the level of support, interactions and research activity within MLO. MLO has also a significant number of postdoctoral fellows, but as in almost all Finnish research units, their number should be increased.

3.3. Output and quality of research activities

The genetic epidemiology section is led by Professor Peltonen (she also has appointment at the University of Helsinki), who must be congratulated on her achievements both at a personal level (President of HUGO, Leader of GenomEUtwin etc.) and as a leader and external fundraiser within MLO. The transition from monogenic disorders, exemplified by past and present Finnish disease heritage work, which is widely recognized internationally as being of very high quality, to that of common and genetically complex disorders has raised questions as to whether the historical advantages of Finnish resources – such as unique population isolates, access to nationwide disease and control cohorts, relative genetic uniformity – would carry over to common disorders. There is a continuing debate as to the advantages and disadvantages of founder populations such as Finland in elucidating the genetic basis of complex disorders. The answers will emerge over the next 5 years but it is already clear that the Peltonen group at MLO is strongly placed to make an impact in this area. This arises firstly from their current success rate in elucidating genetic influences in common disorders, best exemplified by their discovery of genetic variation within USF1 and ORP10 in dyslipidemias, in GPRA in asthmatics and in several genes influencing multiple sclerosis (MHC class II, MBP, PRKCA, C7). The international competition has been intense and they have made excellent use of regional enrichment of cases, such as in autism, schizophrenia and multiple sclerosis. The results clearly show that the group of Professor Peltonen is internationally highly competitive. Secondly, the availability of large and well characterised Finnish population cohorts (e.g. Finnish Birth Cohort, Finrisk, EU twin cohorts) will stand MLO and other researchers in very good stead for both finding and replicating genetic associations, unbiased assessment of genetic effect

sizes and of allele frequencies, and further characterisation of identified susceptibility variants.

Two research groups within the genetic epidemiology section of Professor Peltonen deserve special comment. Firstly, the group of Professor Taipale working on systems biology appears to be innovative and highly competitive internationally. Their use of bioinformatics to predict regulatory sites within the genome, using transcription factors involved in cancer and cell cycle regulation as a model is likely to provide extremely useful skills and software for other groups within and outside of MLO, since the majority of SNPs associated with common diseases appear to be regulatory, although it has proved difficult to establish this unequivocally. A systems biology approach is well suited to the analysis of complex traits involved in human disease and is seen to be a major strength within MLO. Secondly, the quantitative or statistical genetics component under Dr. Perola is an integral part of the genetic epidemiology team, which has increased to 8-10 people due to their success in obtaining external funding, although core funding for this group is limited. Strong statistical genetics is seen to be an essential ingredient in the use of genome-wide association studies and in all future studies of the large epidemiological and twin cohorts.

The majority of the Finnish disease heritage genes have now been identified, which is a major achievement and continues to bear fruit in terms of carrier screening and elucidation of both normal physiological and disease-associated mechanisms. In some cases the studies have continued to elucidate the molecular mechanisms of pathogenesis of the disease. A good example is the APECED gene which has elucidated auto-immune mechanisms relevant to a wide range of such diseases. This work has helped to foster the skills and resources required to characterise genetic variants within disease susceptibility genes that are often of unknown function. This will stand MLO staff in good stead in the future. The identification of 35/36 Finnish disease heritage genes signals the opening rather than the closure of the chapter in which these disorders are elucidated in molecular detail and the public health implications are established for the Finnish population.

Cardiovascular disease remains a major problem in Finland largely due to its association with obesity and metabolic syndrome. The molecular biology of cardiovascular diseases section plays an important role in elucidating such disease mechanisms and links well with the genetic epidemiology studies within MLO. Currently under the leadership of Matti Jauhiainen and Vesa Olkkonen, the section has published a good number of high profile papers and has appropriate international collaborations as well as a prominent role in a variety of clinical trials. They are also well placed to make maximum use of the national epidemiological cohorts with regard to cardiovascular and lipid disorders. Thus the section cardiovascular disease fits very well with the overall profile of MLO.

3.4. National and international co-operation

The level of national and international co-operation is seen to be very high, suggesting that MLO staff is fulfilling the need to interact with other groups to maximize their effectiveness and provide best value for money. In the field of genetic epidemiology, two examples are the linking of national twin cohorts in the GenomEUtwin study, led

by Professor Peltonen, and the Centre of Excellence in Complex Disease Genetics. In cardiovascular disease, the links with University of Oxford (Professor Mark McCarthy) and with the MIT/Broad Institute clearly strengthen MLO research. In the area of "gene to function" there is often the greatest need to develop external collaborations since it is impossible to have all the necessary skills in-house. In some cases, such as the analysis of USF1, in-house expertise in cardiovascular biochemistry and bioinformatics has clearly been a major advantage but MLO have developed a large number of collaborations with national and international partners and so appear to have been very effective in this respect. The move of Professor Peltonen to the Sanger Institute is clearly going to strengthen the links with KTL.

3.5. Resource allocation

The areas of research covered by MLO staff are, in general, receiving strong support by other national governments, often with specific focused initiatives, such as in biobanking and case-control association studies. The latter has proved successful to date in the majority of common disorders investigated with sufficiently large cohorts (e.g. Wellcome Trust Case-Control studies). There would seem to be scope for centring one or more targeted initiatives around MLO activities where Finland has advantages over more diverse populations and health care systems. For example, the availability of good longitudinal data from the population cohorts may lead to better characterised case and control cohorts, with more and better quality quantitative risk factor data. Example might be hypertension or metabolic syndrome, which has become a global epidemic within recent years. Another possible area where there is special Finnish expertise and resources might be in neuropsychiatric disorders. In both cases, very large scale association studies are required with controls that are as well characterised as cases, which has sometimes been the weak link in other such studies (e.g. WTCC studies).

Regardless of whether specific Finnish initiatives are launched in common disorders, association studies are likely to form the backbone of much of the research in genetic epidemiology, cardiovascular and neuropsyciatric disease research over the next 5 years and require suitable core resources. Foremost among such resources must be the availability of high quality statistical genetics and bioinformatics. At the present time the former are largely supported by external short-term funds. The availability of resources to perform high throughput sequencing and animal model studies are expensive but are also essential requirements for future research in this area.

3.6. Research fund raising

MLO staff has been exceptionally successful in raising funds for research, with 55% (see page 5) of research funding being provided by external awards. This reflects very well on MLO staff but also raises some questions about the future. About one-third of external funds came from EU funded projects and it is not clear that this is sustainable in the future. Participation in new ERC funding schemes, licensing of MLO innovations and collaborative agreements with industry are encouraged.

There is a clear plan that FIMM will provide a new building, a high turnover of young group leaders, and a limited number of permanent staff positions, which should maximize research effectiveness, but there appears to be no new funding stream to

support MLO activities. It is therefore essential that the core staff positions discussed below is secured or it could disproportionately compromise much of the work of MLO. It is also very important that MLO continues to develop core facilities and as a member of FIMM participates in the development of new core technologies critically important for the modern biomedical and translational research.

3.7. Development needs, especially regarding processes and organization

The future infrastructure needs of both FIMM and MLO need to be carefully considered. In MLO, the available KTL infrastructure appears to supply many of the needs effectively at the present time but the research environment in molecular medicine is changing rapidly, so that some important changes may need to be considered to maintain international competitiveness. The core MLO infrastructures include genotyping using Sequenom and Affymetrix gene chip platforms; gene expression profiling using Affymetrix gene arrays; and sequencing, currently using an ABI 3730 machine although discussions are underway to obtain a high throughput sequencer such as Solexa; finally, bioinformatic and statistical support. One concern is the need for greater statistical genetic and bioinformatics resources specifically to deal with whole genome and focused SNP association scans in the large national epidemiological cohorts. At the present time, Dr. Perola leads a small group of statistical geneticists about 90% of whom are externally funded and there appears to be a need for core support for database managers, statistical geneticists and programmers, and bioinformaticians in order to cope with the expected deluge of association data. The report refers to the present bottleneck in functional characterisation of locally discovered disease susceptibility genes but we anticipate that a further and severe bottleneck will be in database management, statistical and bioinformatics analysis of association and other gene mapping data. External collaborations with international and national researchers in this area are already in place but it is recommended that in-house expertise be strengthened in this area, perhaps including appointment of a senior figure in statistical genetics.

The issue of the gene characterisation bottleneck in complex disease genetics also needs to be addressed. There appears to be useful synergy between the cardiovascular and complex genetics sections, which links gene discovery with characterisation in this area but the way forward is less clear in neuropsychiatric genetics and other areas where *ad hoc* arrangements can only be made subsequent to gene discovery. In addition, animal models, mainly mouse and *Drosophila*, are being used effectively to complement other functional studies. The continued subsidisation of small animal costs is strongly supported since many researchers at other institutions can no longer afford this type of work and are turning to cheaper models that can be less useful. The use of zebrafish is increasingly used for characterisation of regulatory sequences but this is locally available to MLO researchers. In summary, the future requirements for gene characterisation are both very diverse and impossible to predict in advance so that *ad hoc* arrangements will continue to be necessary.

The appointment of Dr. Kallioniemi as Director of FIMM is likely to change the infrastructure requirements, with some shift in the direction of cancer research. High quality biomicroscopy and confocal imaging, fluorescence activated cell sorting and

laser capture microdissection underpins an increasing amount of modern molecular medicine research so that allowance for purchase and maintenance of such core equipment should be in place to maintain competitiveness. The proposal to purchase high throughput sequencing capacity for genotyping is strongly supported and is more easily justified in the wider context of FIMM. In large scale genomic sequencing FIMM and MLO should collaborate with the Sequencing Center at the Institute of Biotechnology that are using the Roche 454 technology. However, overall sequencing costs are likely to increase with the increased capacity despite substantial reductions in cost per base pair. It is not clear how this will be financed. Sequencing of large, often megabase sized regions is increasingly necessary to identify low frequency variants, to identify signatures of selection and to identify variants underlying linkage or association peaks, all of which are both labour-intensive and costly.

The departure of Professor Peltonen to the Sanger Institute raises questions as to the continuing leadership within the research programme on genetic epidemiology. She will continue in a part-time (20%) capacity at FIMM but it seems to the external evaluators that full-time leadership may be required to ensure the continued success and growth of this area within MLO. Appointment of an internationally recognised human molecular or statistical geneticist would appear to be an important goal.

3.8. Summary of the main recommendations of the evaluation panel

1. Recognizing the many scientific achievements of researchers working at MLO, the panel strongly recommends continuous strong support for all research programmes (genetic epidemiology, systems biology, cardiovascular diseases and Finnish disease heritage) of MLO.

2. As access to up-to-date research equipment and infrastructures is vital for continuous success of MLO the panel strongly recommends KTL to continue its strong support for core facilities required by MLO scientists (in collaboration with the University of Helsinki and FIMM).

3. The panel encourages MLO scientists to increase their participation in technology transfer (patenting, licensing etc.) activities and in research and development agreements with domestic and international pharmaceutical and biotech companies.

4. The panel emphasises that the directorship of the research programme on genetic epidemiology at MLO needs to be solved now that Professor Leena Peltonen will only devote 20 % of her time to the newly organised MLO under FIMM.